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ONCOLOGY

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EDITORIAL

Surgery and different forms of irradiation have long been the methods available for the treatment of malignant tumours and related lesions The complicated expensive apparatus needed for radiation therapy and the technical difficulties including those involving dose calculations have meant that the radiation therapy in particular developed at special units with close cooperation between physicians and physicists Another reason for this concentration to special units was that wider experience could be gained regarding these diseases and their treatment if the patients were assembled at a limited number of hospitals The treatment results could be reviewed with greater ease and the conclusions given a higher degree of validity It became increasingly evident that basic biologic research was a requirement if a deeper knowledge regarding the malignant diseases and the effects of irradiation was to be gained Special departments for radiation physics and biologic research were added to the therapeutic units or set up as separate institutes working in close collaboration with them As time went by various surgical disciplines also became involved in this cooperation

In recent years other methods of treatment such as chemotherapy and hormonal therapy have also been introduced and are playing an increasingly important role either as a complement to the previous methods or as the only method of treatment The significance of immunologic factors in the genesis and treatment of these diseases is becoming more and more evident and in many quarters including the Scandinavian

countries this has led to a widening of the scope of the previous units for radiation therapy to include the new treatment methods while at the same time taking advantage of all the organizing and therapeutic experience accumulated at those centres Many of the old units have been turned into oncologic centres in which representatives from different specialities collaborate This development will undoubtedly contribute towards increasing our knowledge regarding the malignant diseases and improving the effectiveness of the treatment

The blue series of Acta Radiologica has hitherto been denoted as a series for radiation therapy physics and biology As from 1978 the journal will be published under the designation of oncology This implies more than a mere change of name it means that in accordance with its views on the uniform nature of oncology the journal will welcome articles dealing with all the various areas of this field not only on the different forms of irradiation and radiation physics but also on epidemiologic and clinical aspects of malignant diseases as well as on hormonal therapy chemotherapy immunologic problems and related basic research

Erik Lindgren

FROM THE DEPARTMENTS OF RADIATION THERAPY MEDICINE AND MEDICAL MICROBIOLOGY TURKU UNIVERSITY SF 205 0 TURKU FINLAND

EFFECTS OF IRRADIATION ON THE IMMUNE FUNCTION IN PATIENTS WITH MAMMARY, PULMONARY OR HEAD AND NECK CARCINOMA

E NORDMAN and A TOIVANEN

It has been suggested that normal immune functions are of great importance in the defence against malignant diseases (COTTIER et coll 1974) It appears that the immune surveillance is not only important regarding primary tumors but that the patient s immunocompetence during the disease is also related to the prognosis in established malignancy (HERSH et coll 1974) Therefore much attention has been focused on the possible harmful effects of such treatments as irradiation and chemotherapy The injurious effects of irradiation on the lymphoid cells have been demonstrated by BRAEMAN & DEELEY (1973) COSIMI et coll (1973) BLOMGREN et coll (1974) CHEE et coll (1974) whereas SLATER et coll (1976) have pointed out that the lymphoid system may recover within a few months The greatest number of warning remarks have been published by STJERNSWARD (1974) who has suggested that irradiation may result in increased mortality due to its immunosuppressive effects His results have however been criticized (LEVITT et coll 1976) In spite of extensive investigation regarding the interrelationship between the prognosis of malignant disease and the patient s immune functions the question still remains unsettled and the same is true regarding the immunosuppressive effect of various treatment forms Yet in order to treat malignant diseases effectively this information is of vital importance

This work was supported by a grant from the Finnish Cancer Union Submitted for publication 4 July 1977

The irradiated volume in different types of carcinoma may vary Thus a comparison of patient groups with different tumor types receiving radiation treatment may elucidate the effects of the therapy on the patients immune functions Therefore a number of different parameters illustrating the patient s immune status were followed up to 11 months after irradiation of patients with carcinoma in lung or breast having a large volume irradiated and of patients with head and neck tumors receiving treatment of a smaller volume

Material and Methods

The material consisted of 3 different groups of patients The first group consisted of 13 patients with mammary carcinoma Their ages varied from 31 to 81 years with an average of 55 5 years and the follow up time varied from 4 to 9 months At the time of the last control they all were well and without any sign of a recurrence of the disease

Another group was formed of 11 patients with pulmonary carcinoma Their ages ranged from 29 to 72 years with an average of 57 7 years The follow up period was in one case 11 months and in 5 cases at least 2 months In 5 cases only the first sample before irradiation was obtained as the patients died within 2 months

The third group consisted of 11 patients with carcinoma of the head and neck region of which 6 were laryngeal and 5 oropharyngeal The age of these patients varied from 43 to 84 years with an average of 62 5 years and the follow up period was from 3 to 22 months In one patient only the first sample before the initiation of therapy was obtained as the patient died before the end of treatment Four patients remained well at the end of the follow up

Radiation treatment The cases with mammary carcinoma received cobalt irradiation to the parasternal and supraclavicular lymph nodes to a dose of 40 to 45 Gy in 4 weeks Additionally 45 Gy of electrons was delivered to the chest wall

The patients with pulmonary carcinoma were irradiated with an MeV linear accelerator to a dose of 55 Gy usually including the bronchial tumor and the upper part of the mediastinum

The treatment of the head and neck tumors was delivered according to an individual treatment plan with a cobalt equipment to a tumor dose of 55 to 60 Gy in 6 to 8 weeks

Follow up The parameters followed were the peripheral blood lymphocyte count, the percentages of E rosette forming cells (T cells) and EAC rosette forming cells (B cells) (STJERNSWARD et coll 1972 BLOMGREN et coll) and their ratio the lymphocyte in vitro proliferative responses to phytohemagglutinin (PHA) concanavalin A (Con A) and purified protein derivative (PPD) Samples were obtained before the initiation of the irradiation at the end of it and thereafter in connection with the

in about 6 months Recent observations at this hospital suggest that cytostatic treatment with 5 fluorouracil may in some patients cause a depression of immune functions reducing the host resistance to the tumor (NORDMAN et coll 1977)

The main interest was to compare the effect of irradiation in the lymphoid system of three patient groups with different types of carcinoma In the cases with pulmonary and mammary carcinoma the irradiated volume involves a large amount of bone marrow lymph nodes the thoracic duct and also the thymus In patients with head and neck tumors the amount of lymphoid tissue exposed to the irradiation is considerably smaller

The present results suggest that the patients with head and neck tumor i e with a smaller area irradiated did not have as strong an immunosuppressive effect from the therapy as did the other two groups The responses to PHA Con A and PPD remained at a higher level than in the other two groups and the recovery of responses occurred earlier In the third sample taken about 3 months after completion of the therapy the values in patients with head and neck tumor were already at the same level as before the treatment The patients with mammary carcinoma had rather high PHA and Con A values in the fourth sample but PPD responses remained at a lower level even in the fifth sample The patients with pulmonary carcinoma had a remarkably low response to all mitogens

In summary the results of the present investigation confirm the previous observations of the immunosuppressive effect of radiation therapy and also indicate that the suppression is rather long lasting although recovery does occur Furthermore it appears that in cases with a smaller volume irradiated the suppressive effect is slighter and of shorter duration

SUMMARY

The immune functions in patients with mammary pulmonary or head and neck tumors were investigated after irradiation The treatment caused an initial lymphopenia and long lasting depression in the lymphocyte proliferative responses to PHA Con A and PPD The percentages and the ratio of E and EAC rosette forming cells remained unchanged

ZUSAMMENFASSUNG

Die Immunfunktionen nach der Bestrahlung wurden bei Patienten mit Brust Lungen- oder Kopf-Nacken Tumoren untersucht Die Behandlung verursachte eine initiale Lymphopenie und eine langanhaltende Erniedrigung in der proliferativen Reaktion der Lymphozyten gegenuber PHA Con A und PPD Die Prozentwerte und das Verhältnis von E und EAC rosettenbildende Zellen blieben unverändert

RÉSUMÉ

Les fonctions immunitaires de malades atteintes de tumeur du sein du poumon de la tête et du cou ont été suivies après irradiation Le traitement provoque une lymphopénie initiale et une dépression durable des réponses prolifératives des lymphocytes au PHA Con A et PPD Les pourcentages et le rapport des cellules formant des rosettes E et EAC sont restés inchangés

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The main interest was to compare the effect of irradiation in the lymphoid system of three patient groups with different types of carcinoma In the cases with pulmonary and mammary carcinoma the irradiated volume involves a large amount of bone marrow lymph nodes the thoracic duct and also the thymus In patients with head and neck tumors the amount of lymphoid tissue exposed to the irradiation is considerably smaller

The present results suggest that the patients with head and neck tumor i e with a smaller area irradiated did not have as strong an immunosuppressive effect from the therapy as did the other two groups The responses to PHA Con A and PPD remained at a higher level than in the other two groups and the recovery of responses occurred earlier In the third sample taken about 3 months after completion of the therapy the values in patients with head and neck tumor were already at the same level as before the treatment The patients with mammary carcinoma had rather high PHA and Con A values in the fourth sample but PPD responses remained at a lower level even in the fifth sample The patients with pulmonary carcinoma had a remarkably low response to all mitogens

In summary the results of the present investigation confirm the previous observations of the immunosuppressive effect of radiation therapy and also indicate that the suppression is rather long lasting although recovery does occur Furthermore it appears that in cases with a smaller volume irradiated the suppressive effect is slighter and of shorter duration

SUMMARY

The immune functions in patients with mammary pulmonary or head and neck tumors were investigated after irradiation The treatment caused an initial lymphopenia and long lasting depression in the lymphocyte proliferative responses to PHA Con A and PPD The percentages and the ratio of E and EAC rosette forming cells remained unchanged

ZUSAMMENFASSUNG

Die Immunfunktionen nach der Bestrahlung wurden bei Patienten mit Brust Lungen oder Kopf-Nacken Tumoren untersucht Die Behandlung verursachte eine initiale Lymphopenie und eine langanhaltende Erniedrigung in der proliferativen Reaktion der Lymphozyten gegenuber PHA Con A und PPD Die Prozentwerte und das Verhältnis von E und EAC rosettenbildende Zellen blieben unverändert

RÉSUMÉ

Les fonctions immunitaires de malades atteintes de tumeur du sein du poumon de la tête et du cou ont été suivies après irradiation Le traitement provoque une lymphopénie initiale et une dépression durable des reponses prolifératives des lymphocytes au PHA Con A et PPD Les pourcentages et le rapport des cellules formant des rosettes E et EAC sont restés inchangés

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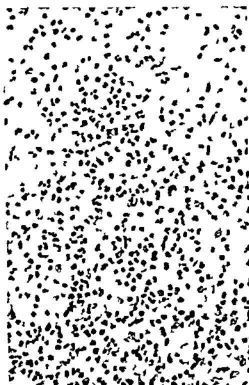


Fig 1

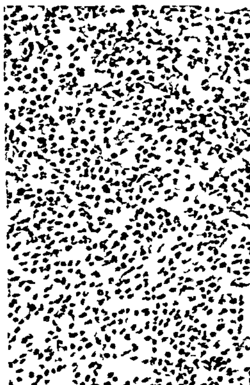


Fig. 2

Fig 1 Predominance of eosinophilic granulocytes (→ → →) Multifocal bone involvement of histiocytosis X No residual disease after radiation therapy Follow up for 3 years Hematoxylin Eosin 225

Fig 2. Predominance of histiocytes (→ → →) with scanty eosinophilic granulocytes (→) Disseminated histiocytosis X The patient died within 2 years Hematoxylin–Eosin 225

Table 1

Age and sex distribution of 27 patients (13 females and 14 males) Figures in parentheses indicate deceased patients

Years	No of cases
0–4	11 (6)
5–9	2
10–19	7
> 20	7 (3)



Fig. 3

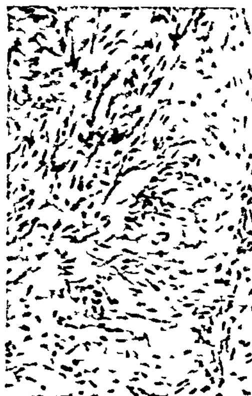


Fig. 4

Fig. 3. Moderate amount of eosinophilic granulocytes, histiocytes and fibrous tissue (+ +). Hematoxylin-Eosin × 225.

Fig. 4. Solitary bone focus of histiocytosis X with severe fibrosis ( ) indicating healing. The patient is well and without new lesions after surgical treatment. Follow up for 9½ years. Hematoxylin-Eosin × 225.

Table 2

Histiocytes, eosinophils, lymphocytes and amount of fibrous tissue in non-fatal and fatal cases

	Alive	Dead
Histiocytes 0	4	1
Histiocytes	14	8
Eosinophils 0	8	9
Eosinophils	10	0
Lymphocytes 0	15	7
Lymphocytes	3	[illegible]
Fibrous tissue 0	14	6
Fibrous tissue	4	3

Table 3

Eosinophilia in bone lesions correlated to non fatal and fatal cases

	Cure within 1½ years	Prolonged course (more than 1½ years)	Dead
Eosinophils 0 –	4	4	9
Eosinophils – +/+ + +	9	1	0

Table 4

Eosinophilia in bone lesions correlated to extent of disease Figures in parentheses indicate deceased patients

	Bone lesion		
	Solitary	Multifocal	In connection with extraosseous lesion
Eosinophils 0/+	2	4 (1)	11 (8)
Eosinophils + +/+ + +	8	2	0

The clinical notes were reviewed with special reference to (1) age and sex of the patients (2) treatment, (3) extent of disease whether a solitary bone focus multifocal bone involvement or more extensive disease involving soft tissues and (4) observation period and the duration of the disease (whether clinical cure of the primary attack was achieved in less than one and a half years or later) The histologic findings were then correlated to (1) the extent and (2) the duration of the disease

Results

The age and sex distribution is given in Table 1 The patients were treated as follows 21 patients were irradiated (6 in combination with surgery and 4 in combination with steroid or chemotherapy) 5 were treated with surgery only and one patient received no treatment Mean survival from the clinical onset of the disease in the 9 deceased patients was 15 months (range 4 to 50 months) Among the surviving patients 10 had solitary bone lesions The mean observation period was 5 2 years (range 0 2 to 15 years) Five patients had a multifocal bone lesion mean observation period 5 7 years (range 2 to 11 years) and 3 patients had both a bone lesion and a soft tissue lesion the observation period being 2 3 and 4 years respectively

The various cellular elements and the amount of fibrous tissue appear in Table 2

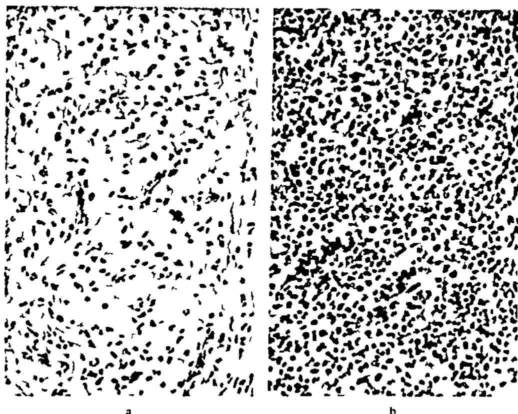


Fig. 5. a) Foam cells from a skull lesion. b) Predominance of proliferating histiocytes ( ) and scanty eosinophilic granulocytes ( ). The patient died within . years. Hematoxylin-Eosin. . 5

and in Table 3 the eosinophilia in the bone lesions is correlated to the fatal and non fatal cases.

The eosinophilia in the bone lesions is correlated to the extent of the disease in Table 4. In the 2 patients with a solitary bone lesion and 0 eosinophilic granulocytes a marked fibrosis was found, indicating healing.

The amount of lymphocytes, histiocytes or fibrous tissue was not found to be correlated to the clinical course or the anatomic extent of the disease.

Examples of the different microscopic appearances are illustrated in Figs. 1 to 5. Foam cells (Fig. 5 a) were only found in 2 patients—in one with a prolonged clinical course and in one who later died of disseminated disease. Cells possibly representing low-differentiated histiocytes (Fig. 5 b) were observed in 2 patients, both died.

Discussion

It is well known that the solitary eosinophilic granuloma of bone has an excellent prognosis in contrast to the rapidly progressive syndrome of Letterer-Siwe. Th

combined concept of histiocytosis X therefore tends to obscure the fact that it covers several different diseases Furthermore various microscopic appearances with gradual transitions probably representing different phases in the diseases have been described Thus Engelbreth Holm et coll (1944) described four phases (1) the hyperplastic proliferative phase (2) the granuloma phase (3) the xanthoma phase and (4) the fibrous (or healing) phase On the other hand Avioli et coll (1963) only separated two phases (1) a cellular proliferative lesion and (2) a fibrotic lesion However no prognostic information was reported concerning the relative amount of the various cell types

As appears from Table 2 the amount of lymphocytes and histiocytes in the bone lesions had no prognostic significance and fibrosis occurred both in surviving and deceased patients

However moderate or marked eosinophilia (+ + or + + +) dominated in non fatal cases (Tables 2 3) especially when clinical cure was achieved early Moderate or marked eosinophilia is clearly associated with solitary bone lesions (Table 4) whereas eosinopenia often is present in cases with multifocal and extraosseous lesions

A decrease in tissue eosinophils in bone lesions on corticosteroid therapy has been reported by Avioli et coll The present material included only bone biopsies before treatment

Obermann (1961) reported an inconstant correlation of foam cells tissue eosino phils and fibrosis with the clinical course However large aggregates of eosinophils indicated a more favourable course Nyholm (1967) emphasized the importance of microscopy of bone lesions especially in differentiation between eosinophilic granu loma and Letterer–Siwe disease

Recently Newton & Hamoudi (1973) distinguished two distinct types of histio cytosis X one with a malignant course (type I) and one with a benign course (type II) The type I lesion consists of infiltrates of mature histiocytes without necrosis fibrosis eosinophils and giant cells The type II lesion is characterized by infiltration of histiocytes with large numbers of eosinophils and giant cells fibrosis and necrosis are often present

The association of eosinophils with a favourable course is also evident from the present material but in contrast to the findings of Newton & Hamoudi fibrosis was found both in surviving and deceased patients Since fibrosis usually indicates healing these patients might possibly have active foci in other not detected locations

SUMMARY

Specimens from 27 bone lesions of histiocytosis X were analysed semiquantitatively before treatment Eosinophilic granulocytes seemed to be the only significant prognostic cell type Absence of eosionphils or only slight eosinophilia in the initial bone lesions were found predominantly in widespread disease with fatal outcome A moderate or severe degree of eosinophilia dominated in solitary bone lesions with good prognosis

ZUSAMMENFASSUNG

Proben von 27 Knochenläsionen von Histiocytosis X wurden halb-quantitativ vor der Behandlung analysiert Die eosinophilen Granulozyten scheinen der einzig signifikante prognostische Zelltypus zu sein Fehlende Eosinophilie oder nur leichte Eosinophilie bei den initialen Knochenveranderungen wurden überwiegend bei ausgebreiteter und wahrscheinlich tötlichen Erkrankungen gefunden Eine mässige oder hochgradige Eosinophilie dominierte bei solitären Knochenveränderungen mit guter Prognose

RÉSUME

Des prélèvements de 27 lésions osseuses d histiocytose X ont été analysés semiquantativement avant traitement Les granulocytes éosinophiles semblent être le seul type de cellules à signification pronostique L absence d éosinophiles ou une éosinophiles discrète dans les lésions osseuses initiales ont été constatés surtout dans l histiocytose étendue et à évolution fatale Une éosinophilie modérée ou élevée prédomine dans les lésions osseuses solitaires qui ont un bon pronostic

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QUANTITATIVE LYMPHOSCINTIGRAPHY FOR DETECTION OF METASTASES TO THE INTERNAL MAMMARY LYMPH NODES

Biokinetics of $^{99}Tc^{m}$-sulphur colloid uptake and correlation with microscopy

K ASPEGREN S E STRAND and B R R PERSSON

Approximately 8 per cent of metastasizing primary mammary carcinoma are at the time of operation spread to the internal mammary lymph nodes but not to the axillary nodes (URBAN & MARJANI 1971) Since biopsy of the internal mammary nodes is not generally performed at the ablation a number of cases are wrongly classified as clinical stage T1N0 Although biopsy of the internal mammary nodes has been carried out in a few series (HAAGENSEN et coll 1972) this is most frequently performed on one side only and not always in all the intercostal spaces Besides the procedure is time consuming and not without risk to the patient

Therefore a safe and simple diagnostic procedure for demonstrating invasion of the internal mammary lymph nodes would be of great value in the treatment of mammary carcinoma It would allow proper clinical staging as basis for a rational treatment At lymphoscintigraphy absence of active colloid accumulation to a lymph node has been considered indicative of malignant invasion (EGE 1976 GÖRANSSON & JONSSON 1974a b) The reliability of this method has been tested by performing a second scintigraphy some days after the first one and comparing

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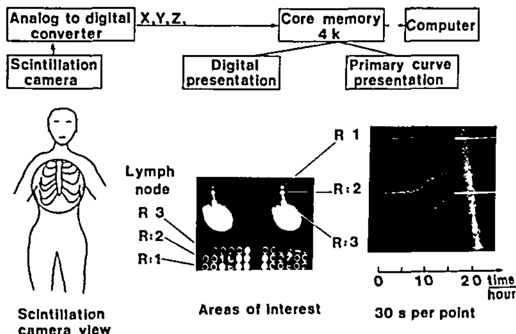


Fig. 1. Scintillation camera and data acquisition scheme. Time–activity curves obtained from patient No. 1 in whom 3 nodes with accumulation were clearly visible. To the right the accumulation curves for the 3 nodes.

the results (EGE). Thus, good to fair reproducibility was observed in 94 per cent of the cases (EGE). A similar reproducibility has also been recorded when hyaluronidase was added to the colloid (GÖRANSSON & JONSSON).

The authors mentioned assumed that no accumulation of the colloid in a lymph node implied gross metastasis to the node. However, it is possible to assume, until proved otherwise, that a non-malignant lymph node sometimes does not accumulate the colloid, or that microscopic invasion does not reduce the uptake. One solution to this essential problem is to perform lymphoscintigraphy and compare the results obtained with those at microscopy of the nodes. Such a procedure was therefore considered necessary before the lymphoscintigraphic method was applied routinely at this hospital.

Material and Methods

Injection procedure. The material consisted of 6 females with primary carcinoma of the breast, one with axillary metastases at the time of operation. The diagnosis was made preoperatively by aspiration biopsy and confirmed postoperatively by conventional microscopy. The $^{99}Tc^m$ sulphur colloid was prepared from 48 µmol of sodiumthiosulfate ($Na_2S_2O_3 \cdot 5H_2O$) and 9 µmol of potassium perrhenate ($KReO_4$) according to PERSSON & NAVERSTEN (1970). The mean particle size of the colloid is 0.6 ± 0.2 µm.

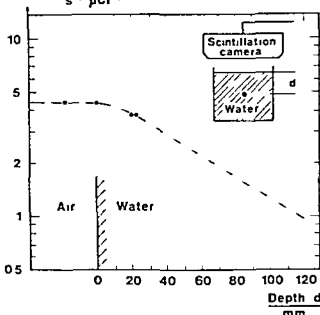


Fig 2. Calibration factor for the lymph node phantom as a function of depth in water. The scintillation camera was equipped with a parallel 16000-hole collimator. A 35 per cent energy window was centered over the 140 keV full energy peak

Biokinetic measurements The general set up of the scintillation camera system appears in Fig 1. The patients were examined in supine position under the scintillation camera equipped with a parallel 16 000-hole collimator. The injection sites covered with 2 mm lead were placed in the lower part of the camera view. Sequential scintigrams at a rate of two frames per min were recorded on a magnetic tape for 1½ h after the injection. When the recording was terminated, curves of activity accumulation were derived from assumed lymph node and background areas.

In order to determine the uptake of the labelled colloid in the lymph nodes quantitatively, corrections must be made for the attenuation of the radiation in the intermediate tissue. This correction was performed using both anterior and posterior measurements two hours after the injection. The count rate observed from the node at anterior view is ϕ_A and the corresponding count rate at posterior view is ϕ_P. If the center of activity lies at a depth d from the anterior surface and l is the thickness of the patient, the count rates can be expressed by the equations

$$\phi_A^d \simeq \phi_A^0 \; f(x_A) \; \exp(-\mu_{eff} \; d) \tag{1}$$

$$\phi_P^{l-d} \simeq \phi_P^0 \; f(x_P) \; \exp[-\mu_{eff} \; (l-d)] \tag{2}$$

where μ_{eff} is the effective attenuation coefficient and ϕ^0 the count rate with the activity free in air, i.e. at zero depth. The distance response function of the scintilla

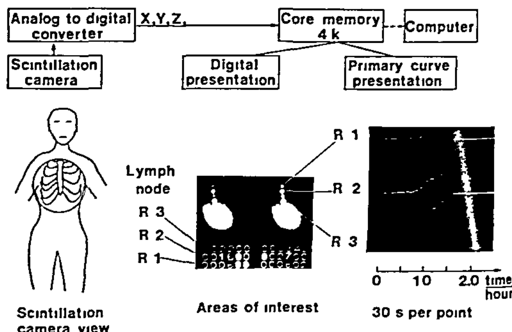


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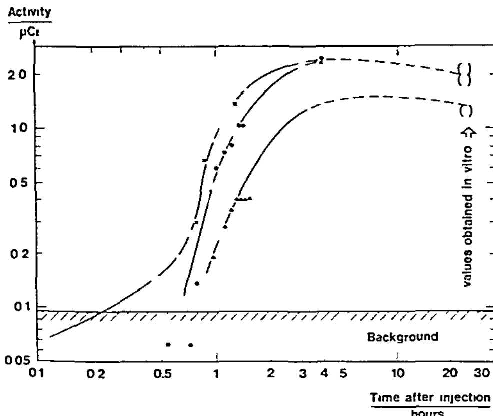


Fig. 3 Genuine uptake of $^{99}Tc^{m}$ sulphur colloid into the right parasternal nodes of patient No 1 The curves are corrected for background activities, physical half life of $^{99}Tc^{m}$ and tissue attenuation Triangles (▲) indicate accumulation into intercostal node No 1 (node between first and second rib), dots (●) indicate incorporation into node No 2 and crosses ( ) into node No 3 The activity injected at the right injection site was 720 μCi

the skin incision to the midline and by undermining the subcutis the three first intercostal spaces could be explored bilaterally along the sternum (HAAGENSEN et coll) The major pectoral muscle was mobilized from medial the intercostal muscles and membranes were incised and the lymph gland was dissected free and removed Before removal the distance between the skin surface and the gland was measured with a ruler Each node was then inserted into a separate plastic test tube with fixative measured for activity then sectioned and stained with haematoxylin-eosin and examined by light microscopy Due to shortage of time or technical difficulties it was not possible to dissect the six intercostal spaces in all the patients However all spaces with scintigraphic activity on the mastectomy side were explored The distribution of the dissected glands from each patient is given in Table 1

Post-operative measurements Four hours after the operation a new static scintillation camera measurement was made to confirm that the removed glands were

Table 2

Results of measurement of depth of lymph nodes from the anterior skin surface by three different methods in patient No. 1

Lymph nodes	Depth (mm)			Calibration factor calculated from anterior and posterior measurements ($s^{-1}\ \mu Ci^{-1}$)
	Antero-posterior view	Lateral view	Operation left side	
R 1	55	(*)	50	2.4
R 2	55	(*)	—	2.4
R 3	29	37	30	3.4

No measurement possible due to background

identical with those recorded before the operation. The activity content of the lymph nodes removed at the operation was measured separately with a NaI(Tl)-crystal (ϕ = 7.5 cm × 7.5 cm) housed in a lead shield. The activity of the node was calculated by comparing the count rate from the node with a standard prepared from a $^{99}Tc^{m}$-colloid vial identical with that used for injection.

Results

The biokinetic behaviour of the uptake of the $^{99}Tc^{m}$ sulphur colloid in the lymph nodes of Patient No. 1 (Table 1) is given in Fig. 3. No significant activity above the background was recorded until ½ h after the injection. The observed uptake is corrected for background activity and physical half life and it thus reflects the biologic behaviour.

The uptake in a node appears to vary with the distance from the injection site, the most superior node having the longest delay until uptake commences. This probably reflects the flow in the lymph vessels and consequently offers a possibility to estimate the flow rate. The activity uptakes into the three nodes 4 hours after injection were 1.5, 2.4 and 2.4 μCi, respectively, or 0.2 and 0.3 per cent of the activity injected at a given site.

The rate of accumulation was much slower in the other 5 patients, and no uptake was recorded during the first 1½ h.

Depth of lymph nodes and accumulation of activity. Depths ranging from 20 to 110 mm from the anterior surface of the thorax were recorded with the anterior and posterior measurements. These depths were confirmed by lateral projections when the site of each node activity was marked on the anterior surface of the thorax with a ^{57}Co point source. Measurements at the operation also confirmed these observations. Results from patient No. 1 appear in Table 2.

Table 3

Distribution of accumulation of $^{99}Tc^{m}$ sulphur colloid into lymph nodes of the internal mammary chain in 6 patients

	Uptake	No uptake	No of nodes
Microscopic normal node	9	7	16
Malignant node	—	3	3

The activities in the lymph nodes 4 h after the injection of the colloid were calculated in 4 patients The values ranged from 0 1 to 2 4 μCi This corresponds to 0 01 and 0 3 per cent of the injected amount of colloid per injection site

Static images Although the amount of activity accumulated in the lymph nodes was small good images were obtained and especially so when the injection sites were covered with lead (Fig 4) The colloid particles used for injection in this patient were of a slightly smaller average size than in previous colloids

Correlation between activity uptake and microscopy of nodes The scintillation camera measurements were compared with the findings at microscopy (Table 3) No activity was recorded in malignant nodes Three such nodes from patient No 2 were massively infiltrated with carcinoma with virtually no lymph tissue left Nine normal lymph nodes where the normality is defined as node without malignant invasion or inflammation *showed substantial accumulation of activity* However no accumulation occurred in six similar normal nodes No histologic differences between those two groups existed No lymph node with both malignant invasion and nuclide uptake was encountered

Discussion

The method described is simple and permits recording of accumulation of nuclide agents into the lymphatics It not only permits static images to be made but also offers possibilities of dynamic examinations i e the rate of the activity accumulation and the estimation of the true activity uptake These parameters may be important in the investigation of the lymphatics in normal and pathologic conditions

Depth determination of the accumulating node is important firstly for the estimation of the tissue attenuation and secondly for proper localisation In the present patients mediastinal nodes were observed and could easily have been erroneously considered as sternal nodes

The static images produced confirm the observations of GÖRANSSON & JONSSON (1974 b) and EGE to the extent that scintigrams of the internal mammary lymph nodes were successfully accomplished However a high frequency (7/16) of absent

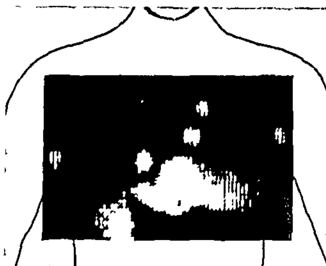


Fig 4 Static image 4 hours after the injection of ^{99}Tc^{m} sulphur colloid in a patient Uptake into 3 parasternal nodes to the left of the sternum and into 2 nodes to the right Accumulation into each axilla from the site of subcutaneous injection 1 cm from the xiphoid process

uptake of the sulphur colloid into normal lymph nodes was detected Since absence of incorporation indicates inflammation or malignant invasion the use of the present ^{99}Tc^{m} sulphur colloid involves a high risk for overdiagnosis When this was revealed further examination of patients was considered unethical which accounts for the small number of patients

When nodes were completely infiltrated no accumulation of activity was observed No node with partial infiltration was found Thus the question whether a partially infiltrated node would incorporate the colloid resulting in an erroneous impression of normality cannot be answered

The frequent failure of normal glands to incorporate the sulphur colloid shows *that a species difference between man and rabbit exists* GÖRANSSON & JONSSON (1974 a) invariably found accumulation in rabbit nodes but this was not so in the present 6 patients Results from animals should thus be applied to human beings with great care

However when the particle size of the colloid was modified by excluding the *perrhenate from the kit and reducing the boiling time from 3 to 1 minute rapid* uptake into lymphatics occurred (Fig 4) This observation as well as the small amount of colloid taken up by the lymph nodes from the site of injection and the large percentage of normal nodes without accumulation indicate that dynamic lymphoscintigraphy with colloids of smaller particle size may be a simple and reliable method of examining the functional condition of the lymphatic system

Further comparative investigations in rabbits of the uptake of colloids of various size in the parasternal lymph nodes confirms this opinion (PERSSON et coll 1978 STRAND & PERSSON 1978)

The present results demonstrate that it is necessary to compare and correlate new diagnostic procedures with pathologic findings

SUMMARY

Dynamic quantitative activity determination and accurate scintigraphic localization of parasternal lymph nodes were obtained from antero posterior measurements with a scintillation camera The scintigraphic observations were compared with microscopy of the nodes removed at operation The $^{99}Tc^m$ sulphur colloid indicated a high frequency (7/16) of absent uptake in normal lymph nodes However the technique used indicates that a similar technique with smaller particle size may be a useful method for proper classification of the clinical stage of carcinoma of the breast

ZUSAMMENFASSUNG

Eine dynamische quantitative Aktivitats Bestimmung und eine genaue szintigraphische Lokalisation der Parasternal Lymphknoten wurden durch antero-posteriore Messungen mit der Szintillationskamera erhalten Die szintigraphischen Observationen wurden mit der Mikroskopie der Lymphknoten die bei der Operation entfernt worden waren verglichen Das $^{99}Tc^m$ S Kolloid wurde in einer hohen Frequenz (7/16) in normalen Lymphknoten nicht aufgenommen Jedoch deutet die verwendete Technik darauf hin dass eine ahnliche Technik mit kleinerer Partikelgrosse eine brauchbare Methode zur richtigen Klassifikation des klinischen Stadiums des Brust Karzinoms sein kann

RESUME

Des mesures faites dans le sens antéro posterieur avec une camera à scintillation a permis la determination dynamique quantitative de l activite et la localisation scintigraphique précise de ganglions lymphatiques parasternaux Ces resultats scintigraphiques ont été compares avec l examen microscopique des ganglions enlevés à l opération Le colloide au $^{99}Tc^m$ S a montre une grande fréquence (7/16) de défaut de fixation dans des ganglions lymphatiques normaux Cependant la technique utilisée montre qu une technique similaire avec une dimension de particules plus petites peut être une methode utile pour une classification adéquate du stade clinique du carcinome du sein

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DOSE AND DOSE RATE IN ^{19}Ir INTERSTITIAL IRRADIATION FOR CARCINOMA OF THE TONGUE

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H Fuchihata and Y Tanaka

Sixty Gy (6 000 rad) delivered in 7 days has been recommended as a standard schedule for the interstitial irradiation of carcinoma of the tongue When the dose rate differed from the standard one the total dose has usually been modified to some extent However this course of action has recently been questioned Therefore the present investigation was undertaken in an attempt to throw more light upon the matter

Material and Methods

From August 1973 to April 1976 73 patients (51 males 22 females) with squamous cell carcinoma of the tongue were treated at this Department of Radiology with interstitial irradiation using ^{19}Ir The patients were classified according to the TNM classification of the UICC (1973) as indicated in the Table The ages of the patients ranged from 22 to 79 years with a median age of 56 Guide gutter technique was used in all cases Single plane implantation was used in 51 patients double plane in 21 and volume implantation in one Hair pin type of ^{19}Ir with one mg Ra eq per cm (60 mg in total) was obtained from the United Kingdom every 4 months on the average The actual dose rate varied because of the relatively short half life of the isotope even if the treatment volume was about the same The treatment regime

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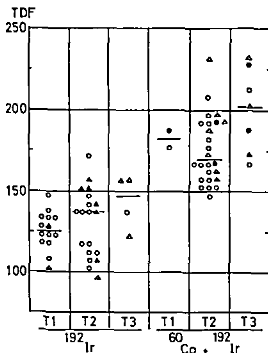


Fig 3 Local prognosis for 71 patients related to treatment method size of tumor and TDF factors o = controlled ● = necrosis ▲ = uncontrolled

irradiated area was analyzed using the TDF factors (ORTON & ELLIS 1973 1974 ORTON 1974) (Fig 3)

In the 19 Ir interstitial group of 14 patients stage T1 12 were controlled and 2 recurred of 19 stage T2 12 were controlled and 7 recurred and of 4 patients stage T3 one was controlled and 3 recurred In the group which received combined telecobalt and ^{192}Ir interstitial irradiation of 2 patients with T1 one was controlled and another developed necrosis of 25 stage T2 16 were controlled 7 recurred and 2 developed necrosis Of 7 stage T3 patients 2 were controlled 3 recurred and 2 developed necrosis Average values of the TDF are 125 137 and 147 for T1 T2 and T3 respectively treated with ^{192}Ir implant and 182 170 and 202 for T1 T2 and T3 respectively treated with telecobalt and ^{192}Ir implant Thus the adjunctive use of external irradiation resulted in a high risk of the local necrosis which is also in accordance with the high TDF values in these cases

The relationship between dose and dose rate appears in Figs 4 and 5 In the ^{192}Ir interstitial group most of the patients received 70 Gy with a dose rate varying from 0 3 to 1 Gy per hour In the group which received combined irradiation most of the patients also received an interstitial dose of 70 Gy from ^{192}Ir with a dose rate between 0 25 and 1 Gy per hour Differences in dose or dose rate within the groups cannot explain the occurrence of necrosis It seems unlikely that a modification of the total dose from 19 Ir by altering the dose rate could have reduced the incidence of late radiation injury

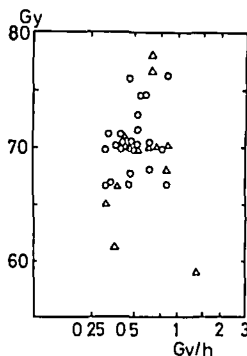


Fig. 4

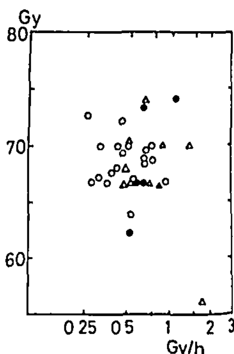


Fig. 5

Fig. 4. Interstitial irradiation with ^{192}Ir alone. Dose versus dose rate. ○ – controlled ▲ – uncontrolled

Fig. 5. Dose versus dose rate. Combined telecobalt and interstitial irradiation with ^{192}Ir. ○ – controlled ● – necrosis ▲ – uncontrolled

Discussion

PATERSON (1963) stated that the standard dose should be 60 Gy in 7 days for treating carcinoma of the tongue with the standard Ra implantation and that the total dose of interstitial irradiation should be adjusted depending upon the actual dose rate. On the other hand PIERQUIN et coll. (1973) reported that no adjustment was necessary at treatment of oral carcinoma with ^{192}Ir implantation when the dose rate varied from 0.25 to 1 Gy per hour. He concluded that a fixed dose of 70 Gy was necessary to control the primary tumour and that an alternation of the dose rate within this range did not influence the frequency of necrosis or recurrence. BARKLEY JR. & FLETCHER (1976) also questioned the classical model of procedure with dose reduction for higher dose rate. They were of the opinion that the dose should not be reduced regardless of the treated volume for obtaining a high percentage of controlled lesions. FU et coll. (1976) reported that relationship between necrosis and dose rate was apparent. AWWAD et coll. (1974) pointed out that the dose reduction was significantly greater in recurrent cases. Previously it has been found that Ra implant alone rarely caused late injury when the dose did not exceed 70 Gy (INOUE et coll. 1976).

An additional external irradiation resulted in a high cure rate in cases with large tumours it is true but also in a high incidence of local necrosis which was explained by the very high tumour dose

Oral hygiene is important for preventing radiation injury to the soft tissue and bone (KEYS & MCCASLAND 1976 REGEZI et coll 1976) CHASSAGNE & WILBAULT (1975) reported that they changed the treatment modalities of large carcinomas of the tongue after 1970 because they found it difficult to control large lesions without occurrence of local necrosis In a series of TxN0 carcinoma of the tongue prophy lactic irradiation of the upper neck with a dose of 30 Gy in 2 weeks could not prevent later development of neck node metastasis (HORI et coll 1977) The present series indicates that the total dose to the primary tumour for interstitial irradiation should be fixed to about 70 Gy when the dose rate varies between 0 25 and 1 Gy per hour An additional external irradiation involves a high risk of local necrosis

SUMMARY

Seventy three patients with carcinoma of the tongue were treated with $^{1\,2}$Ir implantation The total dose for control of the primary lesion without late radiation injury could be fixed to about 70 Gy with a variation of the dose rate between 0 25 and 1 Gy per hour Additional external irradiation without reduction of the dose from the interstitial irradiation involves a high risk of local necrosis

ZUSAMMENFASSUNG

Dreiundsiebzig Patienten mit einem Zungenkarzinom wurden mit ^{192}Ir Implantation behandelt Die Gesamtdosis zur Kontrolle des primaren Tumors ohne Spatschadigung konnte auf etwa 70 Gy festgestellt werden bei einer Variation der Dosisrate zwischen 0 25 und 1 Gy pro Stunde Zusatzliche externe Bestrahlung ohne Reduktion der Dosis der inter stitiellen Bestrahlungsquelle fuhrt ein hohes Risiko einer lokalen Nekrose mit sich

RÉSUME

Soixante treize malades atteints de carcinome de la langue ont été traites par implantation de ^{2}Ir La dose totale pour la guérison de la lésion primaire sans radio-lésion retardee a pu etre fixée environ à 70 Gy avec un débit de dose variable entre 0 25 et 1 Gy par heure Une irradiation externe additionnelle sans réduction de la dose provenant de l irradiation interstitielle implique un haut risque de necrose locale

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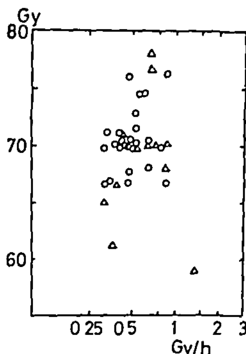


Fig 4

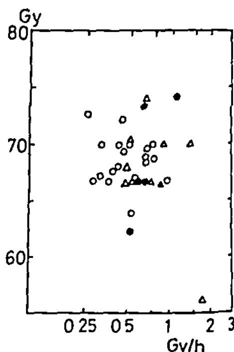


Fig 5

Fig 4 Interstitial irradiation with ¹⁹²Ir alone Dose versus dose rate ○ – controlled ▲ – uncontrolled

Fig 5 Dose versus dose rate Combined telecobalt and interstitial irradiation with ¹⁹²Ir ○ – controlled ● – necrosis ▲ – uncontrolled

Discussion

PATERSON (1963) stated that the standard dose should be 60 Gy in 7 days for treating carcinoma of the tongue with the standard Ra implantation, and that the total dose of interstitial irradiation should be adjusted depending upon the actual dose rate On the other hand PIERQUIN et coll (1973) reported that no adjustment was necessary at treatment of oral carcinoma with ¹⁹²Ir implantation when the dose rate varied from 0 25 to 1 Gy per hour He concluded that a fixed dose of 70 Gy was necessary to control the primary tumour and that an alternation of the dose rate within this range did not influence the frequency of necrosis or recurrence BARKLEY JR & FLETCHER (1976) also questioned the classical model of procedure with dose reduction for higher dose rate They were of the opinion that the dose should not be reduced regardless of the treated volume for obtaining a high percentage of controlled lesions FU et coll (1976) reported that relationship between necrosis and dose rate was apparent AWWAD et coll (1974) pointed out that the dose reduction was significantly greater in recurrent cases Previously it has been found that Ra implant alone rarely caused late injury when the dose did not exceed 70 Gy (INOUE et coll 1976)

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THE PARIS SYSTEM IN INTERSTITIAL RADIATION THERAPY

B PIERQUIN A DUTREIX C H PAINE D CHASSAGNE G MARINELLO and D ASH

The introduction of after loading methods for flexible ^{192}Ir wires in interstitial therapy has brought renewed interest in this modality of radiation therapy through out the world (cf HILARIS 1975) While a major advantage to the therapist and the staff has been the improved radiation protection the use of these techniques has also allowed a new dosimetry to be evolved the Paris System better suited to the charac teristics of flexible wire implants than the previous dosage systems which were associated with rigid sources of finite length (PIERQUIN 1971 DUTREIX et coll in press) The techniques for the use of these methods have been described previously (PIERQUIN 1964 PAINE 1972 PIERQUIN et coll 1977) The purpose of this article is to describe the system of dosimetry which has now been found satisfactory in clinical use for over 15 years and to show the current practice in day to day implant con struction dose calculation and prescription

Although some 90 per cent of the applications are calculated easily by the methods to be described it seems right to say that in a very small number it is not possible to distribute the sources in such a way that this system can be accurately applied usually

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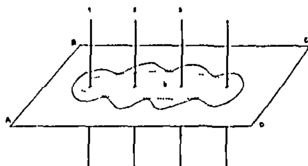


Fig. 1. Four lines (1, 2, 3, 4) transecting the central plane (A, B, C, D) on which dose-calculation is carried out. The basal dose rate (BD) is the mean of the dose rates at a, b and c. The reference dose *rate (85% BD) has an irregular* contour (wavy solid line) and totally encloses the target volume (dotted line).

for reasons of anatomy. For these few cases special calculations are needed, which are sometimes most easily made by computer.

The present article is intended only to be an introduction to the Paris System, a complete account of which *would necessarily be too long for a single article*. The system will be described in detail in two monographs (PIERQUIN et coll. 1978, DUTREIX et coll., in press).

Basic principles

The principles of technique underlying the system are as follows: (1) The active sources should be parallel and straight. (2) The lines should be equidistant. (3) The line or plane on which the mid points of the sources lie should be at right angles to the axis of each source (Fig. 4 a). (4) The linear activity of the lines should be uniform along the length of each line and identical for all the lines. (5) Although in any one implant the sources are all separated equally from each other, a feature of the system is that from one implant to another the source separation may be varied. A minimum of 5 mm separation is acceptable for the smallest volumes, rising to 20 mm for the largest, and (6) For volume implants, the distribution produced in cross section (central plane) should be either an equilateral triangle or a square.

Definitions

Central plane is defined as a plane perpendicular to the sources, which is at right angles to the long axis of the sources, and is situated mid way along their length (Fig. 1). Dosimetric calculations are based on the distribution of sources across this central plane.

Basal dose rate (*BD*) provides a measure of the dose rate in the centre of the treated volume and acts as the basis for dosimetry. It is always calculated from the position of the sources in the central plane and is the minimum dose rate between a pair of

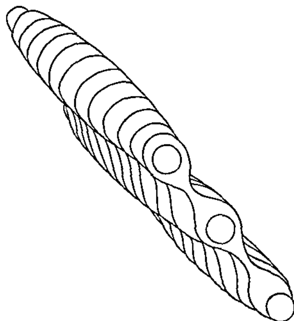


Fig 2 The actual 3-dimensional form of the reference isodose (treatment volume) is that of coalescing cigar shaped volumes surrounding each line source This *overall structure satisfactorily en closes* the usual biologic shape of the tumour and hence target vol umes (Courtesy of L BOUSQUET)

group of sources Where there are a number of sources the basal dose rate for the implant as a whole is taken as the average of its component parts (Fig 1) In practice as will be seen later these points at which the dose rate is minimal are geometrically defined

This concept allows dosimetry to be based on the actual dose rate at the centre of the treatment volume as implanted and not on a hypothetical ideal implant

Reference dose rate (RD) is defined as being 85 per cent of the basal dose rate and is the dose rate used for calculating the total time of the implant (Fig 1) The value has been decided by both clinical experience and theoretical calculation (DUTREIX et coll 1974) Within the limits of source geometry which are used this value leads to an acceptable compromise between too steep a dose gradient in passing from the margin of the treatment envelope towards its interior and too great a ripple of the contour of the treatment envelope

Treatment volume is defined as the volume enclosed by the 85 per cent reference iso dose It is evident that this isodose encompassing the treatment volume has an irregu lar contour when considered in three dimensions it is an amalgamation of several adjacent cigar shaped isodose envelopes (Fig 2) The minimum dimensions of this envelope should correspond as accurately as possible with those of the target volume which it must enclose

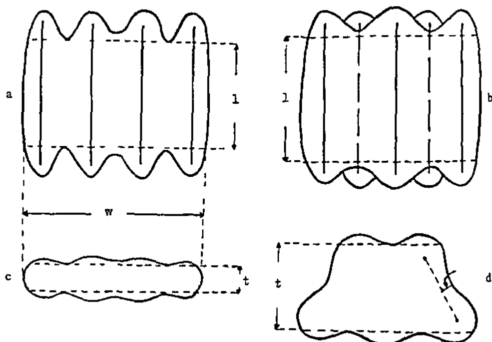


Fig 3 a b) Definition of dimensions of length (l) of the treatment volume for a single plane implant a c) show width (w) c d) thickness (t) In the case of a 2 plane implant the correct definition of length is the minimum distance between reference isodose invaginations between the planes (b) d) Thickness (t) The concept of lateral margin (arrow) For the 2 plane implant illustrated it is the least distance between the reference isodose and a line joining the points at which any two sources intersect the central plane

Relation between source distribution and the target volume

If the general guide lines are followed an implant may be constructed which delivers an homogeneous dose and ensures that the target volume falls within the treatment volume It is nevertheless helpful when performing an implant to have an idea of the relation of the dimensions of the eventual treatment volume to the positions of the source being implanted The general principles on which the system is based were derived from clinical practice but extensive computer calculations have confirmed that the relations used are justified in planning the distribution of an implant so as to ensure adequate margins These relation are not absolute for all cases but depend on the active lengths used and the separation between the sources (PAINE et coll 1969 PIERQUIN et coll 1969 ROSENWALD et coll 1973 WAMBERSIE et coll 1972)

The length of the treatment volume (l) is defined as the smallest distance between the invaginations of the treatment isodose at either end of this volume between the active lines and parallel to them (Fig 3) This is measured in the same plane as the lines if there is only one plane or mid way between the planes if more than one plane

The active sources should be 20 to 30 per cent longer than the target volume at both ends in order to compensate for the fact that the ends are not crossed With hairpins

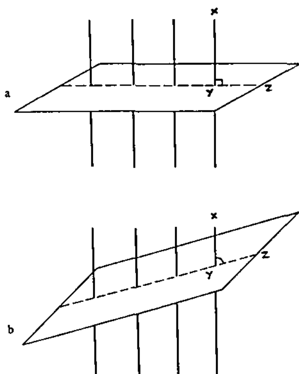


Fig 4 The central plane is correct in (a) where XYZ is a right angle and not in (b) where this angle is acute Otherwise an incorrect source separation will be employed for calculation of basal dose rate

the shape of the pin is such that one end is effectively crossed it is only necessary to add 20 to 30 per cent to the lower end Within this range about 30 per cent needs to be added for short wires and nearer 20 per cent for longer wires

The thickness of the treatment volume (t) is defined as the smallest distance between two parallel planes which are tangents to those isodose invaginations which gives the target volume its least thickness (Fig 3) The thickness in the central part of the implant is clearly greater than the lateral thickness it is found by calculation to be some 10 per cent greater for average implant size

In a single plane implant the thickness of the treatment volume depends on the separation between the sources Thus variation of the separation within the established guide lines can be used to determine the thickness of the treatment volume The thickness of the treatment volume is taken to be approximately 50 per cent of the separation between the sources This varies with the length and number of sources so that the thickness of the treatment volume is 50 per cent of the separation for two lines each 2 cm long and 60 per cent for six lines of 10 cm length In the situation of two planes the thickness is 120 per cent of the source separation when the sources are arranged in triangles and 150 per cent of the separation when they are arranged in squares

The width of the treatment volume (w) need only be considered for calculation of implants in a single plane It is the maximum width of the reference isodose in the central plane (Fig 3) It is equal to the distance between the most lateral sources plus 37 per cent of the separation between the sources added on to each side

Lateral margin In the case of multi plane geometry the concept which is called lateral margin gives an idea of the distance of the outer margin of the treatment volume from the peripheral sources and is defined as the minimum distance measured between the reference isodose and a line joining the points where any two sources intersect the central plane (Fig 3)

The lateral margin is closely related to the separation between the lines but varies very little with the length or number of lines It is roughly 15 per cent of the separation between the sources for multi plane implants constructed in the form of equilateral triangles and roughly 28 per cent of the separation for implants constructed in squares

Separation between sources In using the Paris system finite limits were decided upon within which the source separation must always lie It is difficult to ensure parallelism when the separation is small and minor deviations may give rise to large inhomogeneities in the dose rate Therefore the lowest acceptable separations between sources was considered to be 0 5 cm As the separation between sources increases there is increasing dose gradient between the minimum dose rate between the sources (BD) and that achieved adjacent to them if the high dose volume surrounding each source is too great there is a risk of necrosis In practice the separation is not allowed to rise above 2 cm The guide lines suggested have been decided on the basis of both clinical and theoretical considerations

Identification of the central plane and the distribution of sources within the plane

Different methods may be used to determine the distribution of sources in the central plane of the implant but whichever is used it is important to be sure that the plane used is truly at right angles to the direction of the sources and not oblique otherwise an incorrect separation will be obtained (Fig 4) Whether the actual plane used is exactly half way along the length of the sources or a little way towards their ends is not of much importance in dosimetry as long as the lines are parallel

Direct measurement of source separation is often the easiest and most accurate method for superficial single plane geometry for instance for tumours of the skin The measurement should be supplemented by a photograph or by a conventional film for record purposes

Direct measurement will also be made in those cases in which rigid plastic templates or jigs are used to ensure parallelism of lines in some soft tissue situations such as the

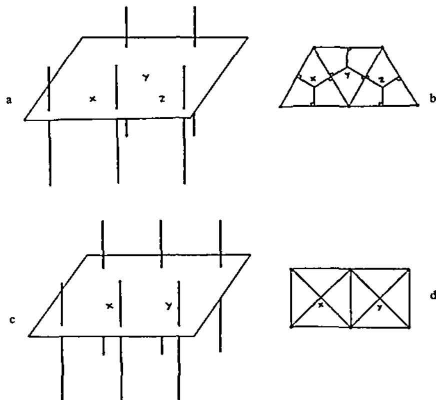


Fig 5 a b) Small 2 plane implant where the sources are arranged in triangles Such triangles should be equilateral or nearly so Whether or not they are strictly equilateral BD is found at points x y and z—where the perpendicular bisectors of the sides of the triangles intersect c d) Acceptable arrangement in squares BD is found in the centre of each square (at x and y)

breast or lip A check must of course be made to ensure that if the measurements are taken from the template itself it remains truly perpendicular to the source lines (Fig 4)

Conventional radiography using orthogonal views at right angles to one another is often used Although this method involves more calculation than is needed in direct measurement or tomography it is satisfactory for some simple geometrics Where many lines are used identification of the same line in both films becomes difficult unless special markers are used Magnification must of course be taken into account In some centres computer programs are available for quick determination of central plane geometry directly from orthogonal films

The technique of shift radiography is an alternative which some have found helpful for source localisation and which depends upon radiography

A geometric reconstruction of the implant can be made in which inactive lines are used to represent the actual positions of the sources The source separations in the central plane are then measured directly

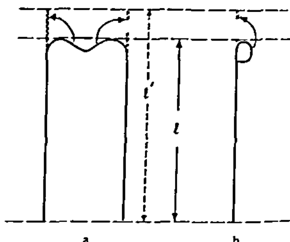


Fig. 6 Convention used to find the radioactive length of a hair-pin which should be employed for calculation purposes a) If the double pin has a useful length (l) of 4 cm, the radioactive length (l') of each of its lines will be taken as half the total length of wire of which the pin is made (9.2 cm) i.e. 4 6 cm. b) The wire making up the single pin is 4 6 cm long, and this value (l') is used for calculation even though the useful length of this pin (l) is 4 cm.

Lastly implant tomography may be employed (PIERQUIN & FAYOS 1962) The aim with this technique is to arrange a tomographic section through the implant which corresponds as closely as possible to the central plane It may be possible to do this with routine sagittal or frontal tomograms but sometimes transverse axial tomography will be needed This demonstrates not only the positions of the sources across the plane of the tomogram but also some associated anatomic structures In using this technique it is vital to ensure that the patient is set up in such a way that the tomographic section is as close as possible to the central plane through the implant (Fig. 4) and it is sometimes helpful to place a thin marker corresponding to the direction of the central plane on the skin in order to help to orientate the tomogram. The magnification of the tomogram must be taken into account in the calculation.

Points at which the basal dose rate (BD) is calculated

The points at which the minimum dose rate between sources are defined geometrically thus in the case of single plane implants the dose rate is minimal at the mid points between the sources in the central plane (Fig. 1)

Where three lines intersect the central plane to form an equilateral triangle BD is taken to lie at the mid point of the triangle where the perpendicular bisectors of the sides intersect (Fig. 5)

If the triangle formed by the intersection of the wires with the central plane is not equilateral, BD is still calculated at the point where the perpendicular bisectors of the sides of the triangle intersect Triangles with an obtuse angle are not acceptabl for proper implant geometry and inevitably result in under-dosage in the region corresponding to the longest side of the triangle

Where two or more planes are used the aim in the construction of the implant is to make the radioactive lines equidistant and thus to create a series of equilateral

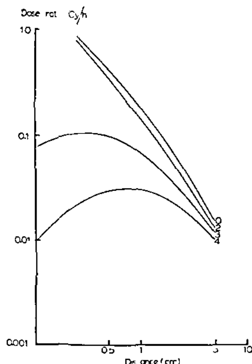


Fig 7 This shows a typical crossline curve from the data of HALL et coll (1966) Crossline O corresponds with the central plane of the Paris system and using that curve dose rates corresponding to increasing distance from the axis of the source may be read The curve shown is for a ^{192}Ir wire of 5 cm length—a different graph is necessary for each active length employed The curves labelled cross line 2 3 4 *also refer to dose rates at distance* from the axis of the wire but starting at a point on the wire which is 2 3 and 4 cm away from the central plane (towards the end of the wire) respectively Data based on wire of linear activity 1 mg Ra—equivalent per cm

triangles In this case the basal dose is the mean of the dose rates in the mid points of all the component triangles (Fig 5)

When four lines transect the central plane in the form of a square the BD may be calculated at the centre of the square However a rectangle is not an acceptable geometric form

As a check upon homogeneity across the central plane the value of BD at the different points at which it is calculated should not vary more than 10 per cent above or below its mean value It will not be found to do so where the implant geometry is according to the guide lines which have been given

Calculation of the dose

The basal dose rate at any of the points described is the sum of the dose rates contributed at that point by each source It therefore depends upon the number of sources their length and distance from the point and their activity

In the special case of double hair pins or loops the value taken for active length is half the total length of wire of which the hair pin or loop is composed thus for a double hair pin of useful length 4 cm (Fig 6 a) composed of 9 2 cm of active wire the active length is taken as 4 6 cm This approximation remains valid as long as the length of a loop or double pin is more than twice the separation of its limbs and

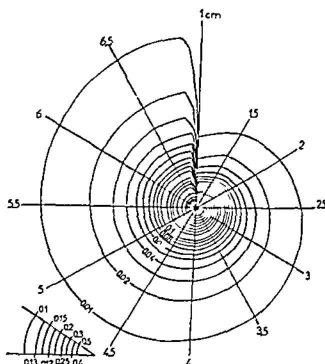


Fig 8 Escargot curve If the centre of the spiral is placed on the point at which a line source transects the central plane reconstruction and the graph is then turned so that the radial line appropriately labelled for the radioactive length of that line passes through the point at which BD is to be found the value of BD at that point is then read directly from the spiral line in Gy/h An Escargot with the same magnification as that of the central plane reconstruction must be used Data based on linear activity of 1 mCi/cm

when the limbs are acceptably parallel In the case of a single pin the active length is taken to be the total length of wire of which the pin is composed (Fig 6 b)

When the distribution of active lines in the central plane has been found their length is known and the sites for calculation of BD have been decided the actual values of BD can be determined by two alternative methods

(1) The distances from each line to each point for calculation of BD (in the central plane) are measured and dose rates then determined by reference to the curves of HALL et coll (1966 Fig 7) Data based on wire of linear activity 1 mg Radium *equivalent per cm—1 68 mCi/cm*

(2) *Dose rate may be directly read on a reconstruction of the central plane source distribution (for instance a tracing of the tomogram) using the graphical template* (escargot) described by SCHLIENGER et coll 1970 (Fig 8) If a magnification factor is present in this reconstruction an escargot of appropriate *magnification must be* employed Data based on wire of linear activity 1 0 mCi/cm A new method of specification for sources used in curietherapy as adopted in 1974 The notion of *apparent* or equivalent activity is replaced by nominal exposure rate i e the exposure rate at a reference distance expressed in mR per hour at one metre (DUTREIX 1974) *The final* value of BD is now obtained by taking the mean of the values obtained at all the points calculated

One further correction must be made to the value of BD so obtained a simple

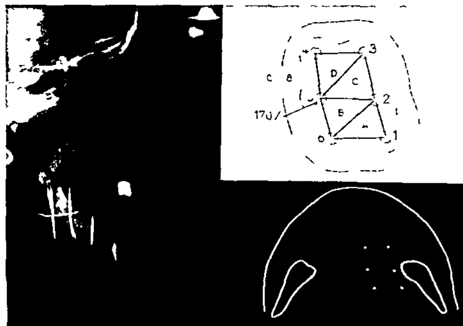


Fig 9 Lateral film and an outline of the tomographic section upon the central plane of an implant of Ir hair pins in the tongue Inset is a labelled diagram of the central plane with some relevant isodoses in relation to the positions of the active lines (1 2, 3 4 5 6) and the points for calculation of BD (A B C D)

multiplication factor for the actual linear activity of wire used This is necessary because the data used in both the above methods for dose rate determination are based on wire of standard activity Furthermore the activity of wire will decay slightly even during the time of application To deal with this latter factor the convention is to take the activity of the wire on the first day of the application then read from the table how much time should be added to the total time of the application in order to compensate for activity decay during this period

The reference dose rate is 85 per cent of the value of BD calculated as mentioned Whilst it is at this reference dose rate that the prescribed dose is delivered it is sometimes of importance in addition to know the dose rates at other points of interest either within or near the treament volume These points may represent either sensitive normal tissue structures low or high spots due to unavoidable imperfections of distribution or necessary extensions of the treatment volume In order to determine the dose at such a point its distance from each source and from the central plane is first determined (sometimes if it is known that such a situation will arise extra tomographic sections will have been taken away from the central plane when this plane itself was being tomographed) then the dose rate can quickly and easily be read from the graphs of HALL et coll and the resulting value corrected for the activity of wire in use

Table

Time to be added to the total time of application in order to compensate for decay during this period

Total time of implant (days)	3	4	5	6	7	8	9	10	11
Time to be added (hours)	1	2	3	4	5.5	7	9	12	14

Biologic correction for dose rate It is not the practice to make any correction for supposed differences in biologic effect due to variations in reference dose rate The limits which are accepted are from 25 to 90 rad/h (0 25–0 9 Gy) which corresponds to an overall implantation time for 65 Gy between 11 and 3 days This consideration is based upon the clinical experience over a number of years No difference in necrosis or recurrence rates was found in cases treated to the same dose between these limits of overall time (PIERQUIN et coll 1973) Because of this even with its relatively short half life of 74 days ^{192}Ir wire remains clinically useful for nearly three months shelf life, a consideration which is of great practical value

Because it is considered that differences in irradiation time between 3 and 11 days do not affect the end result for the comfort of the patient the overall time is generally arranged to lie towards the shorter end of this range (3–6 days) for a radical implant dose of 65 Gy if the source distribution and the activity of the available wire allow

Prescribed dose The dose prescribed is determined as always in radiation therapy by the precise clinical situation As a guide a radical dose using the Paris System would be between 60 and 70 Gy depending on estimated tolerance of normal tissues within and near the treatment volume Where the implant is being employed to give a boost just to the tumour after previous irradiation of a larger volume the dose given by the implant will clearly depend upon the dose previously given To take an example of such a case the whole of a breast might be given 45 Gy by ^{60}Co teletherapy with usual fractionation (e g 2 Gy tumour dose per fraction 5 fractions per week), and the tumour area then receives an added boost at the reference isodose of 30 to 40 Gy depending upon clinical factors

Practical examples

Use of ^{192}Ir pins Fig. 9 shows the lateral film, a tomographic section upon the central plane and a labelled tracing of this plane for a single implant of a carcinoma of the tongue. The active material consists of three double pins whose limbs are 4 cm long, separated by 12 mm. Each therefore consists of 9.2 cm of ^{192}Ir wire (Fig. 6)

$$\text{Average basal dose rate} = \frac{BD_A + BD_B + BD_C + BD_D}{4}$$

$= 0.55$ Gy/h (for wire of activity 1 mCi/cm)

Reference dose rate $= 0.55 \times 0.85 = 0.47$ Gy/h (for wire of activity 1 mCi/cm)



Fig. 10 Film of a breast tumour implanted by steel needles to carry ^{192}Ir wires and a tomogram upon the central plane On the right is drawn a reconstruction of this plane showing the positions of the sources (1 to 7) and the points for calcula tion of BD (A to E) The reference isodose (85) and some other isodoses of interest are also shown

To give a dose of 65 Gy with wire of activity 1 5 mCi/cm (0 9 mg Ra equiv/cm) the pins must stay in for

$$\frac{65}{0\ 47\quad 1\ 5} = 92\ 2\ \text{h}\ (3\ \text{days}\quad 20\ 2\ \text{h})$$

To this must be added 2 hours to take account of decay during period of implantation (Table) The final time is 94 2 hours

Use of uncrossed line sources Fig 10 shows a film of the implant of a breast tumour using steel needles to carry ^{1} Ir wires the separations of the steel needles being fixed by perspex templates The central plane reconstruction is achieved by direct measurement or by tomography and shown in the figure

The implant is composed of 7 active lines arranged in equilateral triangles across the central plane

$$\text{Average basal dose rate} = \frac{BD_A + BD_B - BD_C - BD_D - BD_E}{5}$$

$= 0\ 41$Gy/h (for activity 1 mCi/cm)

Reference dose rate $= 0\ 41 \quad 0\ 85 = 0\ 35$ Gy/h (for activity 1 mCi/cm)

In order to deliver a total dose of 37 Gy with wire of activity 1 5 mCi/cm the wires must be in place for

$$\frac{37}{0\,35 \times 1\,5} = 70\,5 \text{ h (2 days 22.5 h)}$$

To this must be added one hour for decay during the application (Table) making the final time 71 5 hours

Discussion

The purpose of the system presented is to allow the therapist to take advantage of the newer techniques and materials available for interstitial therapy and to apply them easily In order to achieve this some simple basic guide lines have been derived which allow source distribution to be planned without lengthy calculation according to the dimensions of the target volume

The actual dose calculations are made afterwards using the source distribution finally achieved and are not based on any theoretical pretreatment plan Some familiarity with the method together with the help of the escargot curves makes it possible to complete a routine calculation in less than half an hour in most cases.

Because of the ease and rapidity with which the calculations are made it is quite easy to work out the early or late removal of one or more sources which may sometimes be of benefit, particularly where the source distribution is imperfect yet not so poor as to require total reconstruction of the implant

In some situations the dose distribution in planes other than the central plane must be known and in others the anatomic or other reasons prevent the distribution here advocated The methods of dose calculation given here when used with the data of HALL et coll allow points on planes away from the central plane to be quickly calculated A computer may also be helpful in some cases (ROSENWALD et coll.). However the vast majority of implants carried out in clinical practice are suitable for calculation by the methods which have been described and it is perhaps worth remembering that even computer dose calculation cannot bring about a satisfactory dose distribution from a badly constructed implant

Acknowledgements

It is a pleasure to acknowledge the support of the Ciba Foundation in helping Dr D Ash to visit France, and of the Cancer Research Fund Radiotherapy Department, Churchill Hospital, in assisting with communications between the authors We should also like to thank Miss Jeanine Bellec and Mrs Suzanne Highnell for drawing the figures

SUMMARY

As a result of almost 20 years experience using ^{192}Ir wires in interstitial radiation therapy a new method of dose calculation has been evolved, which is especially suitable for the techniques employed Because this system was developed and brought into routine use in Paris, it was called the Paris System. Its basic principles are outlined in this report and the manner in which it is used in clinical practise is explained

ZUSAMMENFASSUNG

Als Ergebnis einer fast 20-jahrigen Erfahrung bei der Verwendung von [illegible]Ir Drahten zur interstiellen Strahlentherapie wurde eine neue Methode zur Dosis-Berechnung entwickelt die besonders fur diese verwendete Technik geeignet ist Da dieses System in Paris entwickelt und routinemassig verwendet worden ist wird es als das Paris-System bezeichnet Die grundsatzlichen Prinzipien werden beschrieben und die Art mit welcher dieses in der klinischen Praxis verwendet wird erleutert

RESUME

Ayant utilise pendant de près de 20 ans des fils de [illegible]Ir en radiothérapie interstitielle les auteurs ont mis au point une nouvelle methode de calcul des doses qui convient particuliere ment pour les techniques employees Comme ce systeme a ete mis au point et introduit en pratique courante a Paris il a ete appele le systeme de Paris Les auteurs decrivent ses principes de base dans cet article et expliquent la manière de l utiliser en pratique clinique

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EXTERNAL SMALL-FIELD IRRADIATION OF CERVICAL CARCINOMA WITH LINEAR ACCELERATOR

Y TANAKA T FUJIWARA and M SAKAGUCHI

For treatment of carcinoma of the uterine cervix combined intracavitary and supervoltage external radiation therapy has been the most common method and excellent results have been reported (ROUSSEAU et coll 1972 BOURNE & ROBERTS 1972) The *intracavitary therapy however is accompanied by various problems such* as poor reproducibility in homogeneous dose distribution which may result in high incidence of injuries to the rectum and bladder even if severe complications are encountered in only about one per cent and exposure of the therapist to radiation

Reports on excellent results of external irradiation alone have appeared but they are fragmentary and the lesions have probably not always been precisely positioned within the irradiated volume (MOTT et coll 1974 TRUMP et coll 1954 MELLOR 1960 BACLESSE 1950)

The roentgen radiation from a linear accelerator is characterized by slight penumbra and minimal scattering Based on these advantages additional small field irradiation was delivered following irradiation of the entire pelvis A new beam directing device was constructed which allows a narrow beam to be directed to the lesion avoiding the bladder and the rectum Since 1967 125 patients have been treated with this technique and have been followed for at least one year The results are now reported

Methods

The method was mainly used in patients with inoperable advanced carcinoma of the uterine cervix most of them in Stage III (Table 1) The radiation procedure employed was as follows

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Table 1

Stage distribution

Stage	No of cases	Per cent
I b	5	4
II	28	22
III	85	68
IV	7	6
Total	125	100

1 Pelvis irradiation The pelvis was irradiated from antero-posterior and postero-anterior opposed fields size 15 cm × 15 cm A mid point dose of about 60 Gy (6 000 rad) was given in 8 weeks, 5 times a week with a 6 MV roentgen beam from a linear accelerator The fields were hexagonal and sufficiently wide to include the common iliac lymph nodes and the cardinal ligament lymph nodes located by lymphangiography The isodose distribution appears in Fig 1

2 Small field irradiation The 6 MV beam was directed to the primary tumour avoiding the bladder and the rectum (SAKAGUCHI et coll 1974) with the new beam directing device This consists of a piece of light alloy about 2 m long supported by a pivot in the center which is movable in any direction and also can slide on the pivot (Fig 2) One end of the rod is equipped with a device for immobilizing the uterus The other end is connected to three linear potentiometers for the x y and z axes. Even the slightest change in the position of the uterus is detected as an electric signal (Fig 3) In determining the volume to be irradiated the bridge circuit is first balanced so that the gauges register zero at a certain position of the uterus With the gauges at zero the device is inserted into the cervical canal and the position of the patient is precisely adjusted (Figs 4 5)

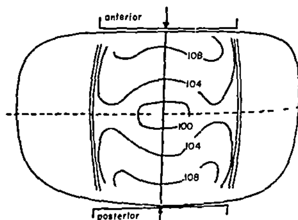


Fig 1 Isodose distribution of pelvis irradiation through two parallel opposing fields with 6 MV roentgen ray (Linac) open fields 15 cm 15 cm TSD 100 cm

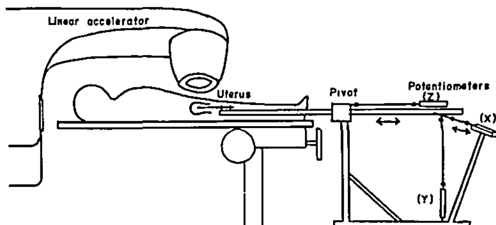


Fig 2 The slightest deviation in the position of the uterus produces a change in the electric resistance of the potentiometer via the long rod

A localization film exposed with the therapy beam appears in Fig 6 After comple tion of the pelvis irradiation a tumour dose of 10 to 15 Gy was delivered three times every second day up to a total dose of 30 to 45 Gy to a reduced volume with the primary tumour in the center The field size 50 to 70 mm × 25 to 40 mm was adjusted to the size of the primary tumour and that of the uterus Moving beam therapy with a lateral pendulum movement of 60 was used in all cases The dose distribution over this small irradiated volume is illustrated in Fig 7 By this means the dose both to the rectum and to the bladder was reduced The total dose in Point A and Point B used in the Manchester system (TOD et coll 1953) was about 105 and 80 Gy respectively

Results

The 125 patients observed for more than 1 year after the irradiation were analysed and the results are given in Table 2 and Fig 8

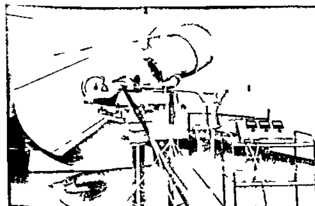


Fig 3 The device for immobilization of the uterus is in serted into the cervical canal with the patient in the lithotomy position

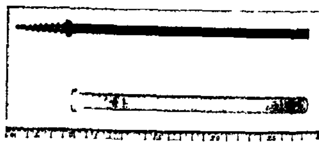


Fig 4 The devices A tapered screw facilitates insertion of the rod into the cervical canal

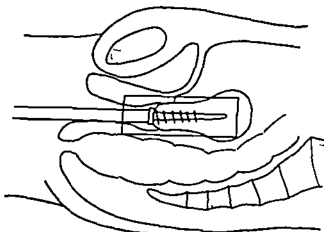


Fig 5 The device is inserted after dilating the cervical canal with Hegar s dilator

Five year results were obtained in 48 25 lived without malignancy none survived with malignancy 20 had died of the malignant disease and 3 of other diseases The five year crude survival rate is 52 per cent The survival rate for patients stage III and IV the majority of the patients was 46 per cent (Fig 8) This result must be regarded as very gratifying in patients with such advanced disease and the method seems especially suitable for stage III cases

Most of the 20 patients who had died of the malignant disease were examined at autopsy as to the presence of malignant cells in the primary lesion (Table 3)

The frequency of late injuries to the patients who additionally received small field irradiation were compared with that in 67 patients given pelvis irradiation alone Virtually no difference between the two groups of patients was found Ileus occurred *in only one patient* who had *received additional irradiation* Cystic hemorrhage occurred in one and rectal hemorrhage in 5 these complications were mild requiring no treatment except in 2 patients with rectal hemorrhage who required blood transfusion Severe cystic and rectal hemorrhages occurred in 2 patients following an additional intracavitary irradiation due to recurrence several months after the primary treatment

Discussion

The roentgen beam from a linear accelerator makes accurate irradiation possible because of its slight penumbra and minimal scattering These characteristics are most

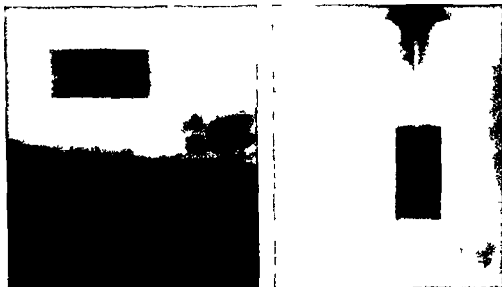


Fig 6 Localization film Device in place (center)

valuable if a small field is irradiated It is impossible to position the lesion accurately in a narrow beam by skin marking Therefore a special beam directing device with high accuracy was designed

With the isodose distribution illustrated in Fig 7 it is possible to irradiate a lesion with a sufficient dose while avoiding excessive irradiation of the bladder and the

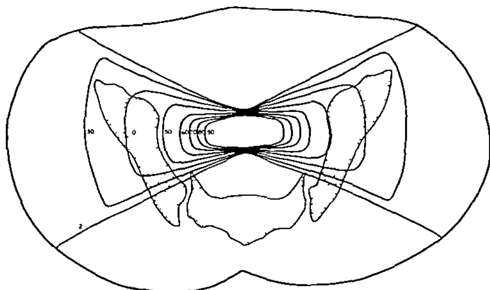


Fig 7 Isodose distribution for a 6 MV linear accelerator using a field size of 60 mm × 25 mm and a 60 lateral pendulum

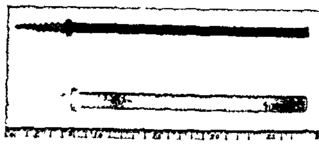


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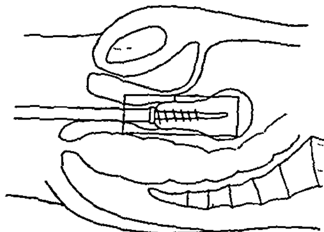


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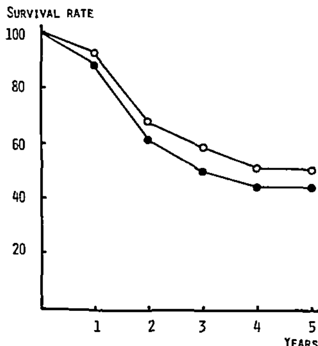


Fig 8 Survival rates (per cent) for stages III+IV (●—●-) and total cases (-○—○-) of cervical carcinoma

postulated for such a treatment are that the primary lesion and its areas of direct and lymphatic spread in the pelvis could be irradiated simultaneously and homogeneously with adequate doses without local overdosage moreover no anesthesia would be needed and there would be little irradiation hazard for the operator and the staff

As a result of small field irradiation with a total dose of 30 Gy following pelvis irradiation with 40 Gy KOECK et coll (1962 1966) achieved a three year survival rate of 69 per cent of the total number of cases a higher survival rate than those reported by other authors CASTRO et coll (1970) reported that a basic tumour dose of 50 Gy in 5 weeks was insufficient to control cervical carcinoma and that patients with limited tumours could be treated effectively with this basic dose to the pelvis supplemented with 20 Gy through reduced fields directed to the cervix

Table 3

Presence of carcinoma in the primary lesion at autopsy

	Stage			Total
	II	III	IV	
Carcinoma	1	4	1	5
No carcinoma	0	10	0	10
Unknown	0	3	2	5
Total	1	17	3	20

The present results were obtained without major radiation injury In the series diarrhea during irradiation was markedly reduced by decreasing the dose from 2 to 1 5 Gy/day Following this reduction of the daily dose diarrhea virtually never necessitated withdrawal of the irradiation Virtually no irradiation injuries could be attributed to the additional small field irradiation and late injuries of the rectum of the bladder or ileus were seldom encountered

MELLOR also stated that supervoltage radiation therapy alone was accompanied by low incidences of injuries to the bladder or the rectum and pelvic fibrosis

Although many of the patients were elderly and had advanced carcinoma favourable results were achieved and the frequency of late injuries was low Probably the technique of external supervoltage irradiation of cervical carcinoma may be further developed improving results Before a definite evaluation is possible particularly as regards the incidences of late radiation sequelae more long term observations are needed

SUMMARY

Since 1966 125 patients with carcinoma of the uterine cervix were treated with a 6 MV roentgen beam from a linear accelerator The pelvis was irradiated with 60 Gy followed by 30 to 45 Gy to a small volume using a lateral pendulum The small field irradiation was performed using a new beam-directing device consisting of a rod with a central pivot Favourable results were achieved despite the fact that most of the patients had advanced carcinoma

ZUSAMMENFASSUNG

Seit 1966 wurden 125 Patienten mit einem Karzinom der Cervix uteri mit 6 MV Rontenstrahlen von einem Linear Accelerator behandelt Das Becken wurde mit 60 Gy bestrahlt und im Anschluss daran wurden 30 bis 40 Gy zu einem kleinen Volumen mit einer lateralen Pendulum Bewegung gegeben Die Klein Feld Bestrahlung wurde unter Verwendung einer neuen Strahlengangrichtenden Anordnung das aus einem Stab mit einer zentralen Drehungsachse besteht vorgenommen Gunstige Ergebnisse wurden erzielt obwohl die meisten Patienten fortgeschrittene Karzinome hatten

RESUME

Depuis 1966 cent vingt cinq malades atteintes de cancer du col de l uterus ont éte traitées par un rayonnnement Roentgen de 6 MV emis par un accelerateur linéaire Le bassin a été irradié par 60 Gy suivis par 30 a 45 Gy a un petit volume en utilisant un mouvement pendulaire latéral L irradiation du petit champ a été faite au moyen d un nouveau dispositif de direction du faisceau consistant en une tige avec un pivot central Les auteurs ont obtenu des résultats favorables bien que la plupart des malades aient un cancer avancé

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CARCINOMA OF THE EYELID

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Carcinoma of the skin is one of the most common forms of malignant tumours. Yearly the Danish Cancer Registry (CLEMMESEN 1976) registers approximately 1 800 new cases, of which about 10 per cent are eyelid carcinoma. In the treatment of this tumour special care must be taken because of the anatomic conditions and the close relation to the eyeball so as to prevent injury to the eye.

At this centre, the treatment of eyelid carcinoma is mainly irradiation. In the 10-year period from first of April 1958 to first of April 1968 274 patients were referred for primary treatment, and the results are now presented.

Material

Eyelid carcinoma is defined here as a malignant epithelial tumour originating from the skin in the area that is bordered by the supra- and infraorbital margins. Malignant melanomas in this area are not included.

The material consisted of 173 men and 101 women (Fig. 1) and most of the patients were between 50 and 60 years of age. Fifty per cent (Table 1) had experienced symptoms or signs for over 1 year and 20 per cent for over 3 years before consulting a physician.

Three patients with multiple tumours have been excluded, thus the material consists of 271 patients.

The area was divided into 4 regions, an upper and lower corresponding to th

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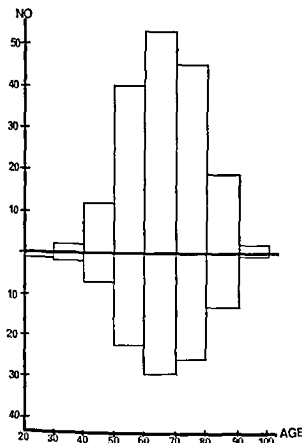


Fig 1 Distribution of age and sex. Upper part 173 males Lower part 101 females.

superior and inferior eyelid and a medial and lateral corresponding to the nasal and temporal commissures

The localisation and extension of the tumour was retrospectively determined by examination of the medical records drawings and photographs 80 per cent were limited to one region while the rest extended to 2 or more regions The most common site was the lower eyelid and nasal commissure where 75 per cent were located (Fig 2)

A percentage of 55 were under 10 mm and only 1 per cent over 30 mm (Table 2) Of the tumours 87 per cent were basal cell carcinoma and the rest were mainly squamous cell carcinoma (Table 3)

Treatment Radiation therapy was given to 256 patients and only 15 patients were primarily operated upon A single dose irradiation was given to 109 patients (42 6 %) and fractionated irradiation to 147 (57 4 %) The single dose treatment was carried out according to the Ebbehoj method which means that the tumour first is scraped to a smooth even surface and then irradiated at 26 or 30 kV with a focus skin distance

Table 1

Duration of symptoms

Years	No of cases
<½	58
½–1	60
1–3	80
Over 3	49
Unknown	27
Total	274

of 10 cm and a 0 2 mm Al filter The total dose has been 39 62 to 47 17 Gy (4 200–5 000 R) measured as surface dose The fractionated irradiation was given at 60 or 70 kV and a focus skin distance of 10 cm As a rule 9 daily fractions were given to a total dosis of 44 39 Gy (4 500 R) surface dose The 3 larger tumours were treated at 100 kV and fractionated over a longer period

A lead capsule 2 mm thick was placed in the conjunctival sac after anaesthesia with a few drops of cocaine mixture to avoid irradiation of the eyeball

Fifteen patients were operated upon primarily Of these 14 had the tumour removed elsewhere and were referred to this centre because at microscopy the excision was not radical with certainty However at the clinical examination no macroscopic tumour was found Thus irradiation was not considered indicated and the patients were controlled only No recurrences have occurred

One patient had a 3 cm × 3 cm basal cell carcinoma in an old burn scar The tumour was removed at a large plastic operation This case differs from the rest of the series, as the patient was young 24 years of age and later developed distant metastases (The case is described in a report on metastasing basal cell carcinoma (LILHOLDT & SOGAARD 1975)

Results of treatment The results are presented in Table 4 No recurrence occurred in 94 5 per cent but only two thirds of the patients were observed for more than 5 years One third died within the first 5 years of other diseases and without recurrences which is explicable as most of the patients were old 39 per cent were over 60 years of age

A local recurrence in 9 patients a new eyelid carcinoma in 4 and 2 patients developed distant metastases Of the patients with local recurrence the primary tumour had a diameter of more than 10 mm in 7 patients they were treated with fractionated irradiation The other 2 patients had a small tumour and were treated with a single dose All tumours with local recurrence except 2 were located in the nasal commissure

The 9 with local recurrence were operated upon and were then free of recurrence The 4 cases with a new eyelid carcinoma were again irradiated and were then also free of recurrence The 2 cases with distant metastases were the young patient with basal cell carcinoma and one with squamous cell carcinoma treated with irradiation

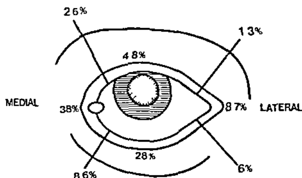


Fig 2 Distribution of tumours in relation to the eyelids

Complications The complications appear in Table 5 Epiphora occurring in 8 per cent was not permanent more a tendency to a watery eye when the patient was submitted to cold and wind

Irradiation necrosis developed in 5 cases These were small ulcerations which healed after conservative treatment *The irradiation scar is healed after 1 to 2 months* Particularly the fractionated irradiation gives an inconspicuous scar with little de pigmentation or epidermal atrophy

Discussion

The present series may to a certain degree be considered as selective as some of the cases *with larger* and deeper *infiltrating* carcinomas possibly are primarily referred to plastic surgery The age and sex distribution corresponds to those of previous Danish reports on carcinoma of the skin (EBBEHØJ 1951 MOSEKILDE 1951 SKOV JENSEN & VETNER 1973) The tumours were located on the lower eyelid and in the nasal commissure in 75 per cent which corresponds to the findings of LEDERMANN (1964) in a material comprising 623 patients with eyelid carcinoma

The present results with reference to freedom from recurrence and complication

Table 2

Size of tumour related to involvement of conjunctival limbus

Size (largest diameter in mm)	No of cases	Involvement of limbus	Per cent
Previous excision	15	4	27
<10	134	35	26
10–20	98	41	42
20–30	20	12	60
>30	3	3	(100)
Unknown	1		

Table 3

Microscopic types

	No of cases	Per cent
Basal cell carcinoma	236	87
Squamous cell carcinoma	25	9
Mixed carcinoma	6	2
Possible carcinoma	2	1
No microscopy	2	1
Total	271	100

Table 4

Results of treatment

	No of cases	Per cent
No recurrence	242	94 5
Local recurrence	9	3 5
New eyelid tumour	4	1 6
Distant metastases	1	0 4
Total	256	100

Table 5

Complications of treatment

	No of cases	Per cent
Ectropion	2	0 8
Entropion	1	0 4
Epiphora	21	8 2
Keratitis	5	2 0
Blepharitis	1	0 4
Temporary radiation necrosis	5	2 0
Total	35	13 8

frequency correlate with the Danish reports on skin carcinoma and the one on eyelid carcinoma by LEDERMANN A primary curative percentage of 95 per cent and a complete cure of 99 3 per cent were found in this investigation LEDERMANN has a primary curative percentage of 92

The 9 patients who had a local recurrence all had marginal recurrences and never central ones In these cases it seems probable that the irradiated area was too restricted and did not include the entire tumour All cases with local recurrence after irradiation were cured by operation

SKOV JENSEN states in an article on single dose treatment that tumours located in

the surrounding parts of the eye and with infiltration of the conjunctival limbus should be treated by the single dose method only if their surface area measures less than 10 mm in diameter Primary operation is indicated instead However satis factory results may be obtained in larger tumours if the treatment is fractionated as demonstrated in the present series LEDERMANN recommended irradiation for all types of eyelid carcinomas except those that are located in the middle third of the upper lid especially because of the relationship of this part of the lid to the cornea In such cases surgery was indicated

Surgery alone has not been used in larger series FREEMANN & KNOX (1964) have collected an American material comprising 1 341 patients with skin carcinoma of which 194 were primarily operated upon 200 were irradiated and 947 were treated with curettage and electro coagulation They found no difference between the results of the treatments except for squamous cell carcinoma over 2 cm in diameter where they found operation to give the best results

However the results are not comparative as curettage with electro coagulation is mainly used for well outlined tumours that are not sclerosive and have not invaded underlying fasciae cartilage or bone

PRÆTORIUS & THOMS (1976) have published a series in which they state that careful scraping of the tumour especially with tumours under 5 mm gives very satisfactory results Curettage with or without electro coagulation on the eyelids should not be recommended because of the close relation to the eyeball and because of a tendency of the tumour to infiltrate the limbus and invade the conjunctiva

Eyelid carcinoma is as a rule a small tumour of low malignancy which can be treated satisfactorily with both surgery and irradiation Both methods give nearly 100 per cent cure and a low complication frequency with correctly performed treat ment Operation entails ordinarily plastic surgery and necessitates hospitalisation whereas irradiation may be given ambulant

As the majority of the patients with eyelid carcinoma are elderly people and as the tumour often is small it is more reasonable to choose irradiation as the primary treatment Operation should be considered for patients with larger and deep in filtrating tumours Recurrence after irradiation should always be operated upon

SUMMARY

A series of 274 cases with eyelid carcinoma 95 per cent irradiated was analyzed The results show that the majority of eyelid carcinomas can primarily be irradiated with satis factory curative and cosmetic results but operation may be considered in larger and deeper infiltrating tumours Recurrence after primary irradiation should be operated

ZUSAMMENFASSUNG

Funfundneunzig Prozent von 274 Patienten mit Augenlid Karzinom wurden bestrahlt Die Ergebnisse zeigen dass die Mehrzahl der Augenlid Karzinome primar bestrahlt werden

kann mit zufriedenstellenden kurativen und kosmetischen Resultaten jedoch kann eine *Operation bei grosseren und tiefer infiltrierenden Tumoren erwogen werden Rezidive* nach primärer Bestrahlung sollten operiert werden

RÉSUMÉ

Les auteurs analysent une série de 274 cas de carcinome de la paupière dont 95% ont été irradiés Évidemment la majorité des carcinomes de la paupière peuvent être traités par une irradiation primaire avec des résultats curatifs et esthétiques satisfaisants mais l opération peut etre envisagée pour les tumeurs plus grandes et plus profondément infiltrantes Les *récidives après une irradiation primaire devraient être opérées*

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PROGNOSTIC SIGNIFICANCE OF HISTOLOGIC SUBDIVISION OF HODGKIN'S DISEASE NODULAR SCLEROSIS

L CIONINI L ARCANINI V MUNGAI G P BITI and R BONDI

The histologic classification of Hodgkin s disease (LUKES 1963 LUKES & BUTLER 1966) as modified at the Rye conference (LUKES et coll 1966) is by now commonly used and has proved to be of relevant prognostic significance

Nodular sclerosis represents in the majority of the published series one of the more frequent types of Hodgkin s disease (LUKES LUKES et coll CROSS 1968 KELLER et coll 1968 COPPLESON et coll 1970 STRUM et coll 1970 BERARD et coll 1971 FULLER et coll 1971 PATCHEFSKY et coll 1973 SCHNITZER et coll 1973) with a frequency up to 74 per cent of all cases (DORFMAN 1971) and is usually associated with a favourable prognosis

Because of this high frequency it has been considered of value to identify some additional histologic features enabling division of nodular sclerosis into subgroups which could better indicate the prognosis

Cellular composition (relative number of mature lymphocytes and Reed Sternberg cells anaplasia of reticulum cells) and amount of fibrosis have been the most used criteria to subdivide nodular sclerosis (CROSS 1968 KELLER et coll 1968 PATCHEFSKY et coll 1973) These authors also analyzed the relationship of the different subgroups with the main clinical parameters of disease and with survival

CROSS on a small group of 29 patients in all stages of Hodgkin s disease with nodular sclerosis (but mainly in stages I and II) found a better median survival

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Table 1

Hodgkin's disease stages I and II. Relapse after treatment according to the initial presentation group (248 cases—all histologic types)

Presentation group	No. of cases	Relapse	
		No.	Per cent
1	8	1	12.5
2	33	5	15.2
3	17	5	29
4	78	41	58.6
5	66	32	48.5
6	46	25	54.3

(8 years 3 months) in the group defined as well differentiated (with prevalence of mature lymphocytes and well developed nodular appearance of fibrosis) than in the group defined as poorly differentiated (2 years 2 months). On the contrary no relationship with the number of involved regions was evident between the two groups.

PATCHEFSKY et coll. combining his series with that published by KELLER et coll. with the same subdivision obtained a group of 177 cases in all stages of Hodgkin's disease with nodular sclerosis. The cellular composition and the amount of fibrosis were examined as independent variables. The cases with more lymphocytes and Reed-Sternberg cells (defined as LP) and those with minimal or mild fibrosis (graded as +1, +2) were found in the earlier clinical stages (I and II) with higher frequency compared with the cases with mixed cellular composition (defined as MC) and advanced fibrosis (graded as +3 and +4). The first two groups were also associated with a better survival. Survival was also calculated for the LP and MC subgroups in stages I and II only to avoid the influence of the different stage composition. This comparison confirmed the better survival of LP cases: the difference between the two subgroups was 12 per cent at 5 years and 22 per cent at 6 years.

All these data, even if suggestive, do not, however, reach statistical significance and further analyses are advisable better to define the existence in the nodular sclerosis group of patients with a different prognosis.

With this intention a group of patients with nodular sclerosis (Hodgkin's disease stages I and II) was retrospectively analyzed and the occurrence of relapses after treatment was correlated with the differing histologic appearances.

The relationship of these histologic features with some other clinical factors was also analyzed: sex, presence of systemic symptoms or signs, and location of the primary involved areas.

The initially involved areas were referred to 6 main presentation groups (Fig. 1). In a previously published series (DE GIULI et coll. 1974) the first 3 groups appeared

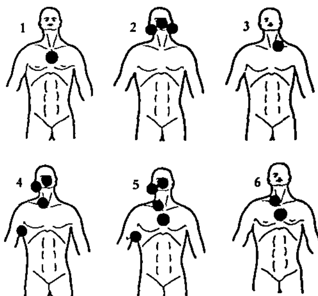


Fig 1 Main sites at presentation Hodgkin s disease stages I and II 1) mediastinum only 2) upper cervical nodes Waldeyer s ring 3) single supraclavicular region 4) multiple superficial areas 5) mediastinum + multiple superficial areas 6) mediastinum + supraclavicular

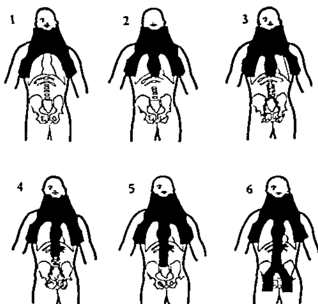


Fig 2 Extension of irradiated areas between 1960 and 1974 1) mantle omitting mediastinum 2) mantle Th10 3) mantle Th10 lymphography with ³²P labelled Lipiodol 4) mantle L2 lymphography with P labelled Lipiodol 5) mantle + paraortic nodes 6) Total nodal irradiation.

Table 2

Distribution of 67 cases of nodular sclerosis according to sex presence of systemic symptoms or signs and initial presentation

Sex	No of cases	Systemic symptoms		Initial presentation groups (no of cases)					
		Absent	Present	1	2	3	4	5	6
Males	24	19	5	1	1	3	5	5	9
Females	43	39	4	4	—	5	11	16	7

Table 3

Subdivision of nodular sclerosis by fibrosis and cellular composition

Fibrosis	LP	MC	LD	No of cases
+1 +2	7	22	1	30 (44 8)
+3 +4	10	25	2	37 (55 2)
Total No of cases	17 (25 3)	47 (70 1)	3 (4 6)	67

to have a much lower incidence of relapse and were associated with a definitely more favourable prognosis A comparison of the relapse frequency in the six groups in a larger series of stage I and II patients appears in Table 1

Materials and Methods

The patients were treated at this Department of Radiology from 1960 to 1974 The total number of stage I and II patients submitted during that period to a radical form of radiation therapy was 248 Unfortunately for only a part of them were the initial slides available several being lost during the flood in Florence in 1966 Histologic revision could be performed in 142 cases and 67 were classified as nodular sclerosis and were included in the present series The staging was revised according to Hodgkin s disease staging classification (Ann Arbor 1971)

The sex distribution and presence of systemic symptoms or signs and presentation appear in Table 2

During the period 1960–1974 the irradiated areas were extended resulting in six alternatives as illustrated in Fig 2 The status of disease was assessed for all patients up to 31 Dec 1975 The minimum follow up was 12 months 85 per cent of the patients were followed for periods of more than 2 years

Table 4

Incidence of relapse after treatment compared with cellular composition and amount of fibrosis

Cellular composition	No of cases	Relapse		Amount of fibrosis	No of cases	Relapse	
		No of cases	Per cent			Number	Per cent
LP	17	3	18	+1 +2	30	8	27
MC	47	19	40				
LD	3	1	33	+3 +4	37	15	41
		0 10 < p < 0 05				0 75 < p < 0 50	

Table 5

Distribution of systemic symptoms compared with cellular composition and amount of fibrosis

Cellular composition	No of cases	Systemic symptoms		Amount of fibrosis	No of cases	Systemic symptoms	
		Present	Absent			Present	Absent
LP	17	1	16	+1 +2	30	4	26
MC	47	7	40				
LD	3	1	2	+3 +4	37	5	32
		0 50 < p < 0 25					

The histologic revision was done at the Department of Pathology University of Florence The pathologists were intentionally not informed on the clinical stage and survival of the patients

In 20 cases in which paraffin blocks with large tissue fragments were available serial sections were prepared in order to determine if the microscopic appearances presented any substantial change in the various sections

The specimens were stained with haemotoxylin-eosin and with the Mallory and Van Gieson methods The specimens were also examined under polarizing light to assess the typical birefringence of the collagen

The amount of fibrosis was classified according to PATCHEFSKY et coll on an ascending scale depending on whether it formed incomplete nodules (+1) or complete nodules involving less than one half of the tissue specimen (+2) or well developed nodules with thick collagen bands (+3 +4)

The cellular composition was graded according to the criteria of KELLER et coll scoring as LP the cases with predominance of mature lymphocytes and few Reed

Table 6

Sex distribution compared with cellular composition and amount of fibrosis

Cellular composition	No of cases	Males	Females	Amount of fibrosis	No of cases	Males	Females
LP	17	7	10	+1 +2	30	15	15
MC	47	15	32				
LD	3	2	1	+3 +4	37	9	28
			0 50<p<0 25				

Table 7

Presentation groups compared with cellular composition and amount of fibrosis

Cellular composition	No of cases	Presentation group		Amount of fibrosis	No of cases	Presentation group	
		1–2–3	4–5–6			1–2–3	4–5–6
LP	17	9	8	+1 +2	30	4	26
MC	47	5	42				
LD	3	—	3	+3 +4	37	10	27
			p<0 001				

Sternberg cells as MC the cases with mixed cell population of eosinophils plasma cells and many Reed Sternberg cells and malignant reticulum cells As LD were classified cases with depletion of mature lymphocytes but still with a nodular appearance

Results

The results of the histologic subclassification appear in Table 3 The two histologic types have been correlated with the relapse frequency and the other clinical parameters separately

The adverse prognostic value of the occurrence of a primary post treatment relapse has already been demonstrated (KAPLAN 1968) Twenty three patients of the present series (34% of total cases) developed a post treatment relapse The distribution of the relapsing cases is compared with the cellular composition and the amount of fibrosis in Table 4

The distribution of systemic symptoms or signs according to the cellular composition and to the degree of fibrosis is given in Table 5 Of the total cases only 9 presented systemic symptoms or signs

Table 8

Extension of irradiated area compared with cellular composition and incidence of relapse

Irradiation area	LP		MC		LD		Relapse/No of cases
	No of cases	Relapse	No of cases	Relapse	No of cases	Relapse	
Mantle omitting mediastinum	—	—	3	2	1	1	3 4
Mantle Th10	7	1	22	12	1	—	13/30
Mantle Th10 lymphography with ^{3} P labelled Lipiodol	2	—	3	1	—	—	1/5
Mantle L2 lymphography with P labelled Lipiodol	3	2	3	1	1	—	3/7
Mantle plus paraortic nodes	4	—	11	1	—	—	1/15
Total nodal irradiation	1	—	5	2	—	—	2/6
Total	17	3	47	19	3	1	

The distribution of patients according to sex appears in Table 6

Table 7 gives the case distribution according to the presentation group Most cases with involvement limited to mediastinum or upper cervical nodes or a single supraclavicular region (groups 1 2 3) belonged to the LP group On the contrary the majority of the MC cases (42/47) had involvement at multiple sites at presentation (groups 4 5 6)

The distribution of cases according to the extension of the irradiated area and to cellular composition appears in Table 8 The number of patients in each group is too small for any significant consideration except in the mantle Th10 group consisting of 30 cases The incidence of relapse was 12/22 in the MC group and 1/7 in the LP group

Discussion

The composition of the present series is comparable to series of nodular sclerosis reported previously

The prevalence of females (ratio 1 97) the frequency of mediastinal involvement (42 cases of 67) and the rarity of constitutional symptoms are confirmed as biologic characteristics of nodular sclerosis

The analysis of the results of the histologic subclassification shows that both the degree of fibrosis and the cellular composition have some correlation with the incidence of relapses after treatment and they seem to distinguish groups of patients with a differing prognosis

Because of the small number of cases the correlations do not have statistical significance but they are supported by the impressive analogy with the data reported by KELLER et coll and by PATCHEFSKY et coll In their series as well as in the present one the cellular composition seems to offer a better characterization of nodular sclerosis than the amount of fibrosis in predicting the post treatment outcome The LP variety appears to be associated with a definitely lower incidence of relapse than the MC variety the significance of the LD variety is uncertain due to its relative infrequency

The advanced degree of fibrosis is associated with a higher incidence of relapse but the difference is not as evident as for the cellular composition

The analysis of the different treatment techniques employed shows that the better prognosis of the LP group does not seem to depend on a more frequent use of a larger irradiated volume furthermore in the 30 cases treated with the mantle Th10 technique the MC cases maintain a relapse incidence higher than the LP cases

The more unfavourable prognostic significance of the MC variety is also confirmed *by the association with other bad prognostic factors such as the presence of systemic* symptoms or signs and the multiplicity of the involved regions at the presentation

The present results seem to support the hypothesis that the M cellularity is an expression of a higher malignancy of the disease

On the contrary no correlation was found between the presence of systemic symptoms or the extension of the initial involvement and the amount of fibrosis as a further suggestion that this histologic parameter has less importance than the cellular composition in the prediction of survival

Addendum in proof

An interesting report is that of COPPLESON et coll (1973) correlating the cellular composition with survival in 358 biopsies of Hodgkin s disease the lymphocyte frequency appeared to have the highest predicting value of prognosis both in the nodular sclerosis and in the mixed cellularity types

SUMMARY

Sixty seven patients with nodular sclerosis (Hodgkin s disease stages I and II) have been subclassified according to the cellular composition and the amount of fibrosis Predominance of mature lymphocytes and rarity of Reed Sternberg cells were associated with less extensive disease at presentation and more favourable outcome A less definite correlation to the amount of fibrosis was found

ZUSAMMENFASSUNG

Siebenundsechzig Patienten mit nodularer Sklerose (Hodgkinsche Krankheit Stadium I und II) wurden entsprechend der zellularen Zusammensetzung und der Menge von Fibrose untergruppiert Die Dominanz von reifen Lymphozyten und die Seltenheit von Reed

Sternberg Zellen waren mit einer weniger ausgebreiteten Krankheit zur Zeit der Diagnose und einer gunstigeren Prognose verbunden Ein weniger gut definitiver Zusammenhang zum Umfang der Fibrose wurde gefunden

RESUME

Soixante sept malades ayant une sclérose nodulaire (maladie de Hodgkin stades I et II) ont été repartis en une sous classification suivant la composition cellulaire et la quantité de fibrose La prédominance de lymphocytes mûrs et la rareté de cellules de Reed Sternberg sont associées avec une maladie moins extensive au moment du diagnostic et comporte un pronostic favorable Les auteurs ont trouvé une corrélation moins nette avec la quantite de fibrose

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Because of the small number of cases the correlations do not have statistical significance but they are supported by the impressive analogy with the data reported by KELLER et coll and by PATCHEFSKY et coll In their series as well as in the present one the cellular composition seems to offer a better characterization of nodular sclerosis than the amount of fibrosis in predicting the post treatment outcome The LP variety appears to be associated with a definitely lower incidence of relapse than the MC variety the significance of the LD variety is uncertain due to its relative infrequency

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Table 1

Magnification as function of object to collimator distance

Distance (cm)	Magnification (arb u.)
8	100
9	90
10	81
11	75
12	70

resolution with magnification (PAIX 1967) Quantitative measurements of the distribution is possible if the gamma camera is interfaced to a computer However problems exist such as variations in the magnification and sensitivity with object to collimator distance and distortions of the true image dimensions due to the finite size of the pinhole diameter

The present investigation was undertaken to develop an improved scintigraphic method for determination of the thyroid volume and estimation of the radiation dose from measurements of the radioiodine distribution within the thyroid gland The distribution was followed in 25 cases from 1 to 72 hours after oral administration of ^{131}I

Material and Methods

A Nuclear Chicago Corp Pho-Gamma III High Performance gamma camera with a tungsten pinhole collimator (4 8 mm diameter) was used for imaging Pinhole collimators of tungsten with 1 and 2 mm diameters were constructed and used for some measurements

Images each containing 20 000 counts were stored on a tape unit (Ampex TM7) by means of the interfaced minicomputer (PDP 8/L Digital Equipment Corp) and the digital system (50/50 Nuclear Data Corp)

The patients were placed in supine position relative to the camera and collimator using three Co point sources placed on a triangle of spots marked on their necks The collimator to-neck distance was kept constant at 8 cm

Images of the thyroid gland were obtained at 1 2¹ 6 24 48 and 72 hours after oral administration of ^{131}I to the fasting patients Images for determination of the thyroid volume were taken at 24 h

The material consisted of 19 patients 6 patients being examined twice on separate occasions making the total number of examinations 25 Thirteen patients had a diffuse goiter while 6 were classified as having nodular goiters on basis of the scintigraphy

FROM THE SECTION OF NUCLEAR MEDICINE THE RADIUM CENTRE ÅRHUS KOMMUNE HOSPITAL DK 8000 ÅRHUS DENMARK

SCINTIGRAPHIC ESTIMATION OF THYROID VOLUME AND DOSE DISTRIBUTION AT TREATMENT WITH ^{131}I

K J OLSEN

Determination of the amount of functioning thyroid tissue and the distribution of radioiodine within the thyroid gland is essential for exact dosimetry in the treatment of thyreotoxicosis Individual dosimetry including measurement of the effective halflife in the thyroid gland forms the basis for evaluation of biologic variations in sensitivity towards radiation and has been found to give the best results in the radioiodine therapy of thyreotoxicosis (GLANZMANN & HORST 1975)

Scintigraphy of the thyroid gland is usually carried out taking a single frontal image The volume of the gland is then calculated using an empirical formula for the correlation between the cross sectional area of the gland in the frontal image and the volume Several formulas have been proposed (KELLY 1954 HIMANKA & LARSSON 1955 SPENCER 1964 MYHILL et coll 1965 SPENCER & WALDMAN 1965 KEZLKA et coll 1973 MANDART & ERBSMANN 1975) but the method has been shown to have large inherent inaccuracy (HULSE et coll 1972) mainly due to the assumption of a relation between the width and the thickness of the thyroid lobes A better scintigraphic method is clearly needed for dosimetry purposes

Changes in the distribution of iodine within the thyroid gland will seriously affect individual dosimetry if these changes occur at a macroscopic level whereas microscopic changes will have little effect on the dosimetry in the case of ^{131}I (ANSPAUGH 1965) but a considerable effect when ^{125}I is used (GLANZMANN & HORST)

Gamma cameras with pinhole collimators are particularly suited for imaging of small objects such as the thyroid gland since these collimators combine high spatial

The investigation was supported by a grant from The Danish Medical Research Council (No 512 3503) Submitted for publication 21 June 1977

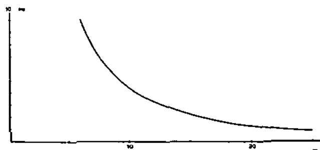


Fig 2 Count rate of IAEA uptake phantom containing ^{1} I as function of distance between phantom and collimator

^{57}Co point sources were used for measuring the changes in sensitivity in a plane parallel to the collimator When the plane was 8 cm from the collimator variations of up to 40 per cent in sensitivity were found without using flat field correction The sensitivity was lowest at the edges of the field of view After flat field correction no variation in sensitivity across the field of view was observed

The resolution of the gamma camera with the 4 8 mm pinhole collimator defined as the minimum distance between point sources where they still were viewed as separate sources was 7 mm for ^{131}I sources 8 cm from the collimator The resolution was improved to 6 mm when pinhole diameters of 2 or 1 mm were used The resolution was higher for ^{57}Co sources than for ^{131}I sources and was much more improved by the 1 or 2 mm pinhole diameters than in the case of ^{131}I

Table 2

Dimensions (cm) and volumes (cm³)

Patient	Right lobe			Left lobe			Volume
	Length	Width	Thickness	Length	Width	Thickness	
1	6 8	2 9	3 9	4 8	1 5	3 5	53
2	5 0	1 9	2 8	4 5	2 4	1 7	24
3	5 8	2 2	3 5	5 8	2 2	3 5	50
4	6.3	4 2	6 3	0	0	0	88
5	5 8	1 6	3 8	3 9	1 6	1 9	25
6	4 4	1 9	2 5	6 1	3 6	3 7	54
7	8 0	4 6	4 5	7 0	3 7	4 5	145
8	3 6	1 9	2 3	0	0	0	8
9	4 9	3 0	3 0	1 4	1 4	1 0	24
10	5 6	2 5	3 0	5 4	2 3	3 5	45
11	4 9	2 0	2 4	5 3	2 0	2 8	28
12	4 4	2 8	5 3	6 0	2 8	6 0	87
13	4 3	2 0	1 8	4 7	2 0	2 0	18
14	4 3	2 2	2 0	6 1	1 8	3 5	30
15	5 6	3 5	3 5	4 8	2 7	3 6	60
16	7 8	2 4	3 9	0	0	0	38

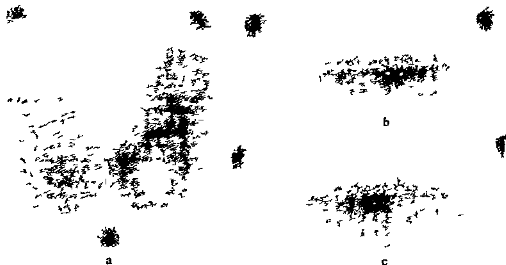


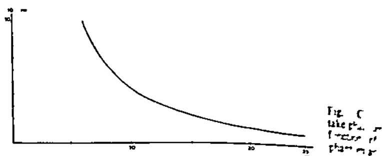
Fig. 1 a) A.p view of thyroid phantom with three ^{57}Co point sources b) Lateral view of thin thyro phantom lobe with two ^{57}Co point sources c) Lateral view of thick thyroid phantom lobe with tw ^{57}Co point sources

The change in magnification with collimator to object distance was measur using two Co point sources 5 cm apart in a plane parallel to the camera crystal fa The results are given in Table 1 for distances used in later experiments

The magnification was also determined in a plane parallel to the crystal face wi ^{57}Co point sources at a collimator to source distance of 10 cm From 0 to 80 per ce of the image field diameter the magnification was constant Above the 80 per ce limit the magnification began to decrease and at the full image field of view it w 6 per cent less than below 80 per cent of the image field

The dimensions of the thyroid gland were measured by taking one a p im with an 8 cm and two lateral images with a 15 cm collimator-to-neck distance ^{57} point sources were imaged under the same conditions i e object to collima distance and provided a scale for measurements of true dimensions This is illustra with the Picker Thyroid Phantom in which one of the lobes is double the thickr of the other (Fig 1) The dimensions measured were larger than the true dimensi by about 5 mm This was found to be due to the use of a pinhole diameter of 4 8 r Better agreement between measured and true dimensions was obtained with pin diameters of 1 or 2 mm This distortion was corrected in subsequent measurem by subtracting 5 mm from the dimensions measured directly from the images A the dimensions of the thyroid lobes had been measured, the volume of the thy gland was calculated using the ellipsoid model (HÜLSE et coll) Results from som the cases appear in Table 2

The change in sensitivity with object to collimator distance was measured u the IAEA Thyroid Uptake Phantom This consists of a 28 ml bottle filled wi solution containing ^{131}I (Fig 2)



⁵ Co point sources were used for measuring the changes in ... parallel to the collimator When the plane was 8 cm from the c... of up to 40 per cent in sensitivity were found without using flat-fie... sensitivity was lowest at the edges of the field of view After flat f... variation in sensitivity across the field of view was observed

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Dimensions (cm) and volumes (cm³)

Patient	Right lobe			Left lobe			[illegible]
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1	6 8	2 9	3 9	4 8	1 5	3 5	51
2	5 0	1 9	2 8	4 5	2 4	1 7	24
3	5 8	2.2	3 5	5 8	2 2	3 5	50
4	6 3	4 2	6 3	0	0	0	88
5	5 8	1 6	3 8	3 9	1 6	1 9	25
6	4 4	1 9	2.5	6 1	3 6	3 7	34
7	8 0	4 6	4 5	7 0	3 7	4 5	145
8	3 6	1 9	2 3	0	0	0	8
9	4 9	3 0	3 0	1 4	1 4	1 0	24
10	5 6	2.5	3 0	5 4	2.3	3 5	45
11	4 9	2 0	2 4	5 3	2 0	2 8	28
12	4 4	2 8	5.3	6 0	2 8	6 0	87
13	4 3	2 0	1 8	4 7	2 0	2.0	18
14	4 3	2 2	2 0	6 1	1 8	3 5	30
15	5 6	3 5	3 5	4 8	2 7	3 6	60
16	7 8	2 4	3 9	0	0	0	38

Macroscopic changes in the distribution of ^{131}I in the thyroid gland were determined by selecting areas of interest and calculating the percentage of the total activity within these for the images at 1 2½ 6 24 48 and 72 hours after oral administration of ^{131}I No significant change in the macroscopic distribution was observed in any of the 25 cases

^{131}I emits both β and γ rays The β rays which have a short range in tissue are responsible for ~90 per cent of the radiation dose (ANSPAUGH)

The dose was calculated from the physical characteristics of the ^{131}I decay using the MIRD system The concentration of ^{131}I in μCi/g was estimated from the images stored on magnetic tape

The 13 patients with diffuse goiter had a homogeneous distribution of ^{131}I and radiation dose In the 6 patients with nodulous goiters large variations in doses within the gland were calculated This is illustrated for case 11 in Table 2 The patient had a total thyroid volume of 28 cm^3 but the main part of ^{131}I was concentrated in three adenomas each having a volume of about 1 cm^3 About 26 per cent of the ^{131}I was concentrated in each adenoma The dose to these nodules was about 7 times the average dose to the gland

Discussion

The present method for determining the thyroid volume is clearly an improvement over the usual calculation of volume from the frontal cross section Results from ultrasonic scanning have shown the latter method to be inaccurate due to large variations in the ratio between thickness and width of the thyroid lobes which is clearly demonstrated in Table 2 The present method overcomes this problem by measuring the three dimensions for each lobe separately It may seem surprising that the thickness can be determined separately for each lobe One explanation is presumably given in Fig 2 which shows that the sensitivity falls rapidly with increasing distance between object and collimator In the lateral views the lobe nearest to the collimator will contribute the major part of the count rate while the other lobe only gives a faint image This is evident in Fig 1 in the lateral view of the thin lobe Another explanation is that the attenuation of the γ radiation in the tissue is larger for the contralateral lobe than for the measured lobe

The present scintigraphic method is estimated to give true dimensions within ±5 per cent In routine use it is important that the scan is carried out under standardized conditions particularly regarding positioning of the patient When the digital system is used as in the present work the background can be measured and corrected individually This permits better delineation of the edges of the lobes

The volumetric method is particularly suited for estimation of the dose distribution

For quantitative measurements it is indispensable that the camera be connected to a computer which can carry out the flat field correction and present the corrected

ellipsoïde L auteur a etudie les problemes qui concernent les modifications de l agrandissement et de la sensibilité en fonction de la distance entre l objet et le collimateur La distribution de l iode dans la glande thyroïde a éte suivie pendant 72 heures après administration orale de ^{131}I dans 25 cas L auteur n a observe aucune modification significative de la distribution dans aucun de ces cas

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PATIENT EXPOSURES AND RADIATION RISKS IN SWEDISH DIAGNOSTIC RADIOLOGY

G BENGTSSON P G BLOMGREN K BERGMAN and L ÅBERG

Medical exposure of patients gives in many countries the greatest artificial contribution to the radiation energy imparted to the population In Sweden and other countries it equals approximately the contribution from natural sources of ionizing radiation and much effort is being devoted to its minimization A useful background for such efforts is knowledge of the radiation doses to patients Radiation levels and their effects have been summarized by the United Nations Scientific Committee on the Effects of Atomic Radiation The latest report was published in 1977 (UNSCEAR) Several recent symposia have also included the topic of patient exposures (IRPA 1977 IAEA 1974 Health Physics Society 1974 Bureau of Radiological Health 1977)

Most of the previous investigations including a Swedish one (LARSSON 1958) have concentrated on gonad doses against the background of possible genetic radiation effects When radiation induced leukemia had become recognized several reports discussed the radiation doses to the bone marrow In recent years attention has also been drawn to other radiation induced malignancies but the corresponding organ doses have only rarely been analysed In the present report the absorbed doses to the thyroid the lung and the female breast are estimated In addition data are given on bone marrow and gonad doses Also included is the energy imparted to the patient which can be estimated from the simple measurement of exposure area product (previously called integral dose) The energy imparted to patients in diagnostic radiology in Sweden has previously been estimated by CARLSSON (1964)

From the Inspection Department National Institute of Radiation Protection S-104 01 Stockholm Sweden Submitted for publication 4 October 1977

Methods

The measurements were made in 13 Swedish hospitals mainly in 1974 but also to some extent in 1973 and 1975 Approximately 1 000 patients were involved

The radiographic techniques employed in those years were rather uniform throughout the country Image intensifier television was generally used Photography of the intensifier image was found to give a negligible part of the collective dose Chest films were normally exposed without fluoroscopy Image intensifiers were being introduced on a small scale for positioning in skeletal examinations and urography Automatic exposure control was generally used in most examinations

Of the many parameters influencing the dose the type of intensifying screen should be specifically mentioned The dominating screen film combination would under optimum conditions require an exposure of 0 1 to 0 3 μCi/kg (0 4–1 mR) to give net density 0 9 Rare earth screens were not used

Examination of gall bladder stomach and colon and special examinations were performed by radiologists Most other examinations were made by specially trained nurses or radiographers

Measurements Before measurements were started at a particular equipment, the potential difference across the roentgen tube was determined using a penetrameter modified from ARDRAN & CROOKS (1968) The total filtration was then approximately determined from measurement of the first half value layer at one or two potential difference values representative of those commonly used with the particular equipment Conversion from half value layer to filtration was made using the tables for constant potential by WACHSMANN & DIMOTSIS (1956)

The exposure area product was measured using flat transparent ionization chambers (180 mm × 180 mm × 17 mm manufactured by Physikalisch Technische Werkstatten) placed on the beam limiting the diaphragm housing Their calibration is traceable to the national Swedish radiation standards laboratory The electrometer used was connected to a recorder enabling separation of the various exposure and fluorography periods in a single examination The potential difference values and cassette sizes used were noted near the recorded trace

The exposure was also measured at various points on the patient using thermoluminescent lithium fluoride dosemeters (3 2 mm × 3 2 mm × 0 9 mm ribbons manufactured by Harshaw Chemical Co) read out on a standard reader (Teledyne model 2910) The dosemeters were calibrated at irregular intervals lying on a wax phantom using a therapy tube at 90 kV with aluminium filtration of 4 mm The same calibration factor was used for all radiation qualities The error due to the energy dependence of the dosemeters was less than ±5 per cent The minimum detectable exposure was about 3 μCi/kg (10 mR) and the reproducibility of the dosemeter readings better than ±6 per cent (95° confidence) At examinations giving low exposures one dosemeter was used to integrate the exposures from several examinations

Calculations The energy imparted is approximately proportional to the exposure area product For the conversion the data by CARLSSON were used strictly applicable to a 20 cm water slab In most of the examinations this should mean a good approximation A thickness of 15 cm and 25 cm respectively would mean a change of the energy imparted per exposure area product by about −7 and +4 per cent, respectively If the primary beam is close to the laterally limiting surface of the body the semi infinite slab approximation used will overestimate the energy imparted by approximately 10 per cent If the radiation beam is outside the surface the overestimation will be even larger With the types of examination concerned this error is estimated to be less than 10 per cent

Thyroid dose A dosemeter (sometimes several) was placed on the laryngeal prominence (Adam s apple) The absorbed dose D in the thyroid was calculated from the measured exposure X using

$$D = CX \qquad (1)$$

The factor $C = 32$ Gy kg C^{-1} (0 84 rad/R) represents a conversion from exposure to absorbed dose in muscle and also contains a correction factor of 0 9 allowing for attenuation in interposed tissue corresponding to about 1 cm The thyroid tissue as well as other soft tissues considered has been assumed to be equivalent to muscle with respect to radiation absorption This introduces a systematic error which is less than 20 per cent in all cases excepting a few extremes for instance at very low potential differences

In a few examinations part of the thyroid is directly irradiated in antero-posterior or lateral projections The dosemeter may then represent the thyroid dose poorly because of the sharp dose gradient Examinations of the dorsal spine and skull are included here Usually the sharp gradient concerns only one of several projections for instance in examinations of the cervical spine This reduces the misrepresentation An overall value of absorbed dose averaged over several individuals is probably representative of the mean thyroid dose but individual values might be misleading due to the method of measurement

Mammary dose The dosemeters were normally placed on the skin in a position considered to be representative of the main part of the breast tissue This was usually about 10 cm from the midline of the body and near the fourth or fifth rib The dose was calculated using eq 1 with $C = 29$ Gy kg C^{-1} (0 74 rad/R) containing an attenuation correction factor 0 8 corresponding to the average attenuation in 2 5 cm tissue This factor is strictly not applicable to posterior irradiations but its use was considered justified since posterior irradiation was estimated to give very small contributions to the total absorbed dose in the dosemeter

In examinations of the stomach and gall bladder the dosemeter was placed on the left and right breast respectively and the mean dose in both breasts was taken

as 0 6 of the dose in the breast where the dosemeter was placed In chest examinations the dosemeter was placed on the breast which in the lateral projection was nearest to the roentgen tube and the same factor of 0 6 was used to give the mean dose

In urography the representativity of the normal dosemeter position was questioned Therefore 3 dosemeters in different positions at a breast were used for the calculation of the mean breast dose at some laboratories The normal position seemed to represent the mean absorbed dose with an uncertainty within a factor of 2 and no attenuation correction factor was applied Nor was it applied in examinations of the small intestine and colon where secondary radiation from rather large distance should have given the main dose contribution

In examinations of the thoracic and lumbar spine the lateral exposure may give rise to large dose differences between the two breasts Unfortunately the dosemeters were not systematically placed on the breast receiving the higher dose The mean value over all laboratories should still represent an average breast dose but individual results exhibit a large spread which may have been enhanced due to the positioning of the dosemeters and are thus not quoted

Lung dose From the exposure area product (when the lungs were in the primary beam) the number and type of exposures the field size and the mammary dose an approximate dose averaged over all of the lung tissue was calculated taking into consideration the approximate volume of lung irradiated radiation quality etc The average attenuation in the thorax was assumed to equal that of 12 cm polymethylmetacrylate at a p or p a projection and 17 cm at lateral projection The calculation was made assuming a typical case based on data from all laboratories and no attempt at detailed calculation was made in the individual cases

Bone marrow dose Detailed calculations of the mean absorbed dose to the whole active bone marrow were only made in a few cases Instead the hypothesis was set up that the mean marrow dose to adults in many examinations could be estimated to a good approximation from the exposure area product XA using

$$D = kXA \qquad (?)$$

where $k = 58$ Gy kg $m^{-2}C^{-1}$ (0 015 rad/(Rdm^2))

This hypothesis is based on the assumption of an approximately uniform distribution of the bone marrow over a projected body area of 0 2 m^2 in a p or p a projections and a mean ratio of absorbed dose at the bone marrow site and exposure at the surface of 11 6 Gy kg C^{-1} (0 3 rad/R) The latter was derived from data by ELLIS et coll The relative dose at lateral exposures was estimated to be 1 5 times lower than at a p or p a whereas the projected area should be correspondingly smaller so approximately the same conversion factor k should apply irrespective of projection The hypothesis was not expected to hold to any good approximation in irra

diations involving arms and legs in which cases it was not tested A first test against detailed calculations in several cases of lung exposures and dental examinations showed an agreement within ±20 per cent Even if this was fortuitous it encouraged further tests which could not due to lack of time be made in the same detail It was decided not to use the suggested approximation in examinations where any indication was found that it would fail by more than a factor of 2 This was the case only in a few types of examination In lumbar spine examinations one half of the value of k was used and in urography one fifth In gall bladder examinations the alleged marrow dose is believed to be an overestimate but the varying practices regarding the exposures make a better estimate impossible In stomach examinations the alleged dose is also believed to be an overestimate With the mentioned exceptions eq 2 could be used for the estimation of mean marrow dose

Testes dose A dosemeter was placed in 2 to 3 cm of thin plastic tubing and taped to the inside of the thigh near the scrotum on male patients The absorbed dose to the testes was calculated from eq 1 using

$$C = 32 \text{ Gy kg C}^{-1} \text{ (0 84 rad/R)} \qquad (3)$$

Ovary dose Excepting colon examinations a dosemeter was placed in 20 cm of thin plastic tubing and its first 15 cm inserted into the rectum The distance between the dosemeter and uterus and ovaries was probably about 5 to 10 cm The basis for the dose calculation was eq 1 with $C = 36$ Gy kg C^{-1} (0 93 rad/R) No further correction was applied for examinations of the colon in which the dosemeter was placed in the top of the special tube used to prevent release of the enema Approximately uniform irradiation of the ovaries uterus and dosemeter site was assumed In some hysterosalpingographies the dosemeter was most often in a position between the ovaries and the radiation source In these cases the measured dose was divided by 3 as an approximate correction for attenuation in interposed tissue A corresponding multiplication by 3 was made in other examinations of the same kind in which the radiation had an opposite direction In examinations of the lumbar hip and spine and in urography a similar multiplication by 2 was made and in pelvimetry 1 3 was used The gall bladder examinations were difficult to assess and no correction was made The alleged ovary dose appears to be rather approximate

Calculation from the exposure area product field sizes and number of exposures was made in examination of dorsal spine pelvis and small intestine

No well founded estimate of ovary dose was made relating to hip examinations

Results and Discussion

The absorbed doses to the individual patients are extremely variable As an extraordinary example the testes dose in lumbar spine examinations varied between 0 2 mGy and 50 mGy i e the highest value is 250 times the lowest In most cases the extremes are found within a factor of 10 A large number of factors influence the

resulting absorbed dose It is obvious that characterization by single numbers, for instance mean values, must involve large approximations Several thousand measurements on about a thousand patients were made in 13 hospitals This enables assessment of the mean absorbed dose in a given body organ at a given type of examination with an overall accuracy of about ±50 per cent. A warning is thus in place concerning too far reaching conclusions for instance relating to time trends of patient doses.

The discussion centers around five major points (1) The spread of doses between individuals an anlysis facilitates the understanding of sampling errors, (2) the possibility of dose reduction deduced from the variations of dose between groups of patients examined under different conditions (3) estimates of collective doses, (4) estimates of the genetically significant dose and (5) estimates of risk for late radiation effects

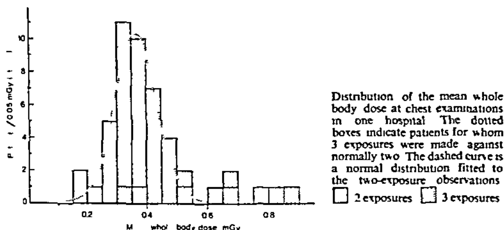
Accuracy of dose estimates Before entering into a discussion on these points, the limitations of the primary dose estimates must be discussed

The physical measurements upon which the patient dose estimates were based could be made routinely with an accuracy of about ±10 per cent Calculations of absorbed dose at the dosemeter site or of energy imparted assuming a patient with a density similar to that of water add an error of about the same magnitude or less. The major uncertainty in the estimate of the dose to an individual patient lies in the transformation from dose at the dosemeter site to actual organ dose. It is sometimes possible to position the dosemeter at a quite representative position. This applies to the thyroid and the testes where the transformation averaged over several patients may be accurate to perhaps 20 per cent, although an error by a factor of 2 might be possible in single patients

The other organs are larger or further away from the dosemeter and the representativity of the dosemeter site consequently poorer The position of the organ in relation to the dosemeter may depend strongly on the positioning of the patient The breast, for instance may be strongly displaced to the side when the patient is resting on one side Attenuation in interposed tissue amounts to about a factor of 2 for each 5 cm and no strict determination of corresponding correction factors was made The mean dose in these organs (breasts, lungs bone marrow and ovaries) should thus have an uncertainty of about a factor of 2 or less as an average over several patients In individual patients the uncertainty may be still higher

In the estimates marked with an asterisk in Table 5 it is not unlikely that the uncertainly might exceed a factor of 2, because of uncertainties in calculations or scarcity of primary data.

Spread of doses between individuals The individual patient s dose is influenced by several factors his body size and constitution the performance of the equipment used, the education and training of the personnel and the method of examination. An example of the distribution of average whole body absorbed dose in ches-



Distribution of the mean whole body dose at chest examinations in one hospital The dotted boxes indicate patients for whom 3 exposures were made against normally two The dashed curve is a normal distribution fitted to the two-exposure observations

examinations is given in the Figure The same equipment and personnel was used for all patients A significant deviation from the normal distribution was found at large patient doses With some patients three exposures were required whereas with most patients two were sufficient If the three-exposure cases are exluded a good fit to a normal distribution is obtained This illustrates that basically a well defined distribution may be present when the number of parameters is limited but as further parameters are introduced the distribution may become odd The average whole body dose in stomach examinations at one hospital with given equipment and personnel followed closely a normal distribution but the energy imparted deviated slightly Neither the chest nor the stomach examinations fitted a log normal distribution A general conclusion from this is a warning against simplifying assumptions about the frequency distributions of patient doses

Individual organ doses may exhibit a quite significant spread (standard deviation above 100°) and strongly depend on for instance the care exercised in field size adjustment The energy imparted is often less variable as is the mean absorbed whole body dose Showing the least spread the latter was chosen for some calculations of patient dose variations With a given set of examinations using given personnel and equipment, the whole body dose in examinations of individual patients showed a relative standard deviation of about 40 per cent Returning to the cited example concerning chest examinations two-exposures gave a standard deviation of 31 per cent while it was about 37 per cent when three exposures were used The difference is barely significant but it hints that the standard deviation may increase as more variables are introduced Similar hints arise from the observation that patient doses from examinations performed by an experienced radiologist may have much less spread (and also lower mean whole body dose) than those by the less experienced radiologist Percentage standard deviations of the mean whole body dose below 20 per cent and above 60 per cent were observed in about 10 per cent of all sets of examinations

Table 1

Unusually wide spread of individual doses in some examination types at one hospital with the same personnel (10 examinations) or at all hospitals considered indicated by the ratio of the mean and the median value

Examination type or organ examined	Dose to	Mean/median		Explanation
		One	All	
Hip	Whole body	1 5		Highest dose 2 times second highest due to one additional exposure
	Testes	1 7		Highest dose 4 times second highest due to one additional exposure
Lumbar spine	*Testes*	3		*Highest dose 3 times second highest* Occurred in two hospitals
Lumbar spine	Ovaries		1 4	Doses at one hospital 2 times higher than average
Urography	Breast	1 7		Highest dose 5 times second highest possibly due to additional exposure
	Thyroid	1 7		*Possibly variations in body weight* and number of exposures
Stomach	Thyroid	5		Highest dose 30 times second highest Fluoroscopy started at the mouth
Stomach	Ovaries	4		Highest dose 10 times second highest Occurred in 2 hospitals
Colon	Testes	3		One group of doses about 10 times higher than the rest
Cholecystography	*Whole body*	1 5	1 3	*Examination often discontinued because of* incomplete contrast filling
Thoracic spine	Testes	3		Highest dose 5 times second highest
Thoracic + lumbar spine	Testes	2		Highest dose 6 times second highest due to one patient weighing 144 kg
Thoracic + lumbar spine	Whole body	2		Highest dose 3 times second highest due to one patient weighing 144 kg

The instances of wider spread are particularly interesting Several causes add to the total spread It is therefore tempting to expect a normal distribution of the doses Exceptionally high and also sometimes very low recorded doses indicate however very skewed distributions A mean or median value and a standard deviation then give a very incomplete idea of the distribution One example concerns a set of lumbar spine examinations where 11 examinations gave testes doses below 6 mGy one gave 15 mGy and one 45 mGy Another pertains to urography where the central mammary dose was in 12 examinations below 7 mGy and in one 30 mGy Exclusion of the highest value in these cases reduces the mean to about one half

The deviations from the normal distribution can also be illustrated by the difference between median and mean value As a rule the mean whole body dose is

between 0 9 and 1 3 of the median supporting the hypotheses of a fairly normal distribution In a number of cases the difference between median and mean was larger (Table 1)

Possibilities of dose reduction A major reason for determining patient doses is the hope for results implying possibilities of dose reduction The existence of a wide spread of the dose to different groups of patients leads to the hypothesis that with suitable measures the dose in every group of patients can be reduced to that of the group exhibiting the lowest dose

Significant efforts may be made towards reducing the dose of all groups to a value below a maximum acceptable dose This decision may in any particular case be based on a measurement of the mean dose to a sample group of patients The sample mean will have a statistical uncertainty which has to be kept reasonably small To give an example the double standard error of the mean value will be about 25 per cent if this mean is based on measurements on 10 patients and the standard deviation of a single measurement is 40 per cent which is typical in the case of mean whole body doses In this case a measured mean dose 25 per cent above the maximum acceptable does not necessarily imply that the true mean is unacceptable nor need a value 25 per cent below the maximum be acceptable Whether dose reduction measures should be initiated depends on such things as the cost of these measures the cost of further measurements which would lower the uncertainty and the strength of the recommendation to keep the doses below the maximum acceptable To aid such decisions the possibilities of reducing the uncertainty interval of the sample measurement will now be discussed It is important to point out that such a reduction is not intended to improve the estimate of the collective dose

Table 2 illustrates a number of sets of measurements including several of the sets exhibiting the widest spread of individual doses If all examinations performed at a certain laboratory during a limited time period are analysed the double standard error of the mean value of the set often approaches 100 per cent Frequently the set includes a single strongly deviating observation Such observations get reduced significance if a log normal distribution is assumed (GADDUM 1945) The mean value of the logarithms corresponds to the geometrical mean of all observations and this is assumed to represent more normal observations It was found that with the small number of observations made in a practical situation another definition of normal observations gives about the same (within 35°) mean value as the geometrical mean while being more easily understandable The two middle quartiles of the observations rejecting the 25 per cent highest and the 25 per cent lowest observations were used (Table 2) In comparison with using all observations the double standard error of the mean value was never significantly increased In many cases it was significantly reduced and at most it amounted to 80 per cent

The table permits comparisons within nine pairs of technicians radiologists or hospitals If all examinations are included three pairs are found in which the ratio

Table 2

Examples of differences in mean exposures in certain organs between various sets of examinations The comparison is made on the basis of exposure at the dosemeter site or mean body exposure in units of mR Little attention should be given to the absolute values The notation $680_{6\ 0}$ indicates an exposure of 680 mR with 690 mR as the double standard error of the mean value The hospitals where the examinations were made and the staff members who performed the examinations are represented by numbers in the third column

Examination type or organ examined	Dose	Hospital or examiner	No of exam	Exposure		
				Arithmetic mean mR		Geometric mean mR
				All examinations	Middle quartiles	
Lumbar spine	Testes	Technician 1	13	680_{690}	280_{40}	300
		Technician 2	6	57_{11}	55_{11}	56
Lumbar spine	Ovaries	Hospital 1	12	260_{0}	260_{20}	240
		Hospital 2	6	640_{90}	$650_{2\ 0}$	560
Lumbar spine	Testes	Hospital 1	20	140_{14}	53	51
		Hospital 2	6	41_{21}	38_{18}	34
Urography	Breast	Technician 3	11	170_{0}	170_{30}	141
		Technician 4	*13*	*600_{400}*	*400*	*450*
Urography	Thyroid	Technician 5	5	47_{13}	44_{13}	45
		Technician 6	8	73_{39}	61_{27}	55
Urography	Ovaries	Technician 3	9	430_{20}	430_{0}	380
		Technician 4	11	680_{140}	710_{60}	640
Stomach	Ovaries	Radiologist 1	8	290_{440}	67_{45}	58
		Radiologist 2	21	84_{25}	71_{20}	58
Colon	Testes	Radiologist 1	11	$3\,100_{21\ 0}$	$2\,100_{1\,700}$	1 400
		Radiologist 3	6	580	350_{60}	4 0
Cholecystography	Whole body	Hospital 2	10	220_{0}	210_{60}	190
		Hospital 3	16	110_{40}	100_{20}	90

of the highest and the lowest dose is significantly exceeding 1 (it is about 2) If only the two middle quartiles are included the confidence of the significance for these three pairs is increased and two more pairs are added In either case 1 6 is the lowest ratio significantly different from unity This supports the belief that a reliable comparison of the normal dose to groups of patients can be made using the two middle quartiles However a warning is indicated against too optimistic a view on demonstrable differences between sets of measurements Many observations of the order of 100 will be required to demonstrate clearly differences below 25 per cent between normal groups of individuals In evaluating possibilities of dose reduction it must be carefully considered whether differences by a factor of 2 or less are really significant

These observations have a bearing also on the follow up of dose reducing measures It is suggested that a possible dose reduction be considered either on a sample of the continuous flow of patients using the middle quartiles of the observa tions or on patients selected according to pre-determined criteria restricting some of the most important causes of dose variations for instance the body weight or the number of films exposed

While such procedures may facilitate relative comparisons they may be strongly misleading as to absolute dose levels Table 2 shows that the mean dose of the normal group may be less than one fourth of the mean dose in the group For the assessment of collective dose or risk it is very important that the odd observations are not excluded

With these limitations of the data thus established the mean values of all measured doses are presented in Table 3 It must be borne in mind that these represent only approximately the mean values of the populations from which the sets of examina tions are drawn The table also gives the lowest mean value recorded for one hospital and the highest as fractions of the overall mean This indication of the spread in the results is given only if measurements were made in at least 2 patients at each hospital and at least 3 different hospitals were involved

The hypothetical possibilities of dose reduction may be examined using Table 3 The ratio of the highest and the lowest mean group dose is in the range 1 5 (energy imparted dorsal spine examinations) to more than 60 (testes dose dental intraoral exposures) Since the significance of ratios of 2 or below is questionable only ratios of 3 or more will be discussed (Table 4) Half of all observed ratios relating to energy imparted and thyroid and mammary dose are around or above 3 the corresponding figure for ovaries and testes being 4 and 10 respectively It may thus quite safely be concluded that significantly reduced patient doses are generally possible As a first approximation it may be estimated that the doses might be reduced from the overall mean value to the lowest value observed at any hospital It is scarcely probable that this dose is too low to give sufficient information since almost all of the radiology is supervised by well trained radiologic specialists Often the overall radiation level can be reduced as indicated by the energy imparted Frequently careful attention to shielding can significantly reduce the dose to various organs involved If the lowest observed value could be attained the data in Table 3 indicate that it should be possible using available techniques to reduce the energy imparted thyroid dose mammary dose and ovary dose to the Swedish population to about one half and the testes dose to less than one third of the present average level

Collective doses The Swedish Board of Health and Welfare collects quite detailed information on the frequency of various types of radiologic examinations excluding the bulk of dental and mass miniature chest examinations To calculate the collective dose their statistics from 1973 were used multiplied by 1 34 to correct for an

Table 3

Mean values of all measured doses The ratios min/mean and max/mean refer to the lowest value for one hospital and the highest as fractions of the overall mean Results with an indication of spread are given only if at least 2 patients were included at each of 3 or more hospitals

Examination type or organ examined	Energy imparted (mJ)			Absorbed dose (mGy)					
				Thyroid			Breast		
	min/ mean	mean	max/ mean	min/ mean	mean	max/ mean	min/ mean	mean	m
Hip and femur (upper third)	0 71	120	1 21		—			—	
Pelvis	0 46	87	1 38		—			—	
Lumbar spine	0 51	410	1 78	0 58	0 16	1 42	0 37	1 20	2
Urography	0 71	510	1 16	0 51	0 38	1 40	0 13	5 40	1
Stomach and duodenum	0 29	310	1 49	0 51	0 29	4 2	0 44	1 00	
Small intestine		210			—			—	
Colon	0 63	600	1 56	0 58	0 10	2 3	0 83	0 27	1
Hysterosalpingography	0 56	90	2 6		—			—	
Cholecystography cholangiography	0 46	90	1 08	0 66	0 03	1 33	0 35	0 15	3
Thoracic spine	0 83	210	1 21	0 55	13 0	1 23	0 62	1 70	
Lungs (full size) ribs	0 61	21	1 35	0 35	0 17	2 3	0 54	0 55	1
Lungs (photofluorography)	0 50	73	3 0		1 00			2 00	
Lungs plus heart	0 55	40	1 28	0 48	0 24	1 38	0 45	0 61	1
Dental (intraoral single exposure)	0 15	2	3 5	0 4	0 03	3		0 005	
Cervical spine	0 62	18	1 27	0 35	1 40	1 57		—	

estimated loss at certain hospitals and other installations In addition were used estimates on dental and mass miniature chest examinations made in cooperation with various bodies involved military as well as civilian The resultant frequencies per 1 000 population given in Table 5 are believed to be correct within about ±10 per cent The frequency of pelvimetry is based on a separate estimate with about the same accuracy

Table 5 also includes the overall mean doses per examination (including all extreme values) from Table 3 as well as some results (based on the present measurement) which were not included in Table 3 These can be used for estimation of collective dose only if the hospitals visited can be assumed to represent the whole population of hospitals To some extent this may be justified since an effort was made to select hospitals with good as well as bad practices according to the evaluation However it was often found to be incorrect and the systematic error in the collective dose due to incorrect sampling of the hospitals may be considerable It may however be small in comparison with the statistical error of the results If the sampling had be-

Table 3 (*cont*)

dose (mGy)

		Bone marrow			Ovaries			Testes		
m an	max/ mean	min/ mean	mean	max/ mean	min/ mean	mean	max/ mean	min/ mean	mean	max/ mean
—			2 50			—		0 63	15 00	2 3
—			1 90			1 90		0 23	3 10	2 3
<1 00			4 10		0 49	6 20	2 1	0 09	1 80	2.3
<1 00			2 40		0 57	8 80	1 33	0 18	3 30	3 0
<0 50			4 20		0 15	0 56	2 1	0 58	0 16	1 63
—			3 50			1 80			—	
<0 70			9 40		0 57	7 00	1 99	0 29	5 30	3 9
—			1 70		0 53	5 90	1 67		—	
<0 10			1 53		0 54	0 24	2 3	<0 50	0 06	3 7
8 00			4 70			<1 00			—	
0 8			0 29			—			—	
3 5			0 9			<0 1			<0 1	
1 2			0 54			—			—	
0 001			0 01		<0 1	0 0001	6	<0 1	0 0001	6
—			0 38			—			—	

random the overall mean would typically have a double standard error of about 40 per cent. The calculated collective dose for a certain organ summed up for all types of examinations may be in error somewhat but not much less since different hospitals were sampled for different types of examinations

In several cases Table 5 has been supplemented by doses from the estimate in the ICRP publication on patient protection (ICRP 1970) or estimates based on knowl edge of the techniques used As a rule these supplementary data only weakly influence the collective dose The classification follows essentially that of the ICRP–ICRU (1957) except for the splitting of three categories into two classes each considered justified by the examination frequency and dose conditions Thus the small intestine group was divided into small intestine and colon the chest group into chest and chest plus heart and the skull and cervical spine group into its two types Special examinations such as more extensive angiographies were considered to have an insignificant influence upon the collective dose therefore they were included in other groups for instance nephroangiography in the urography group

Table 3

Mean values of all measured doses The ratios min/mean and max/mean refer to the lowest recorded value for one hospital and the highest as fractions of the overall mean Results with an indication of spread are given only if at least 2 patients were included at each of 3 or more hospitals

Examination type or organ examined	Energy imparted (mJ)			Absorbed dose (mGy)					
				Thyroid			Breast		
	min/ mean	mean	max/ mean	min/ mean	mean	max/ mean	min/ mean	mean	[illegible]
Hip and femur (upper third)	0 71	120	1 21		—			—	
Pelvis	0 46	87	1 38		—			—	
Lumbar spine	0 51	410	1 78	0 58	0 16	1 42	0 37	[illegible]	[illegible]
Urography	0 71	510	1 16	0 51	0 38	1 40	0 13	5 40	[illegible]
Stomach and duodenum	0 29	310	1 49	0 51	0 29	4 2	0 44	1 00	[illegible]
Small intestine		210			—			—	
Colon	0 63	600	1 56	0 58	0 10	2 3	0 83	0 77	[illegible]
Hysterosalpingography	0 56	90	2.6		—			—	
Cholecystography cholangiography	0 46	90	1 08	0 66	0 03	1 33	0 35	0 15	[illegible]
Thoracic spine	0 83	210	1 21	0 55	13 0	1 23	0 62	1 70	
Lungs (full size) ribs	0 61	21	1 35	0 35	0 17	2 3	0 54	0 55	[illegible]
Lungs (photofluorography)	0 50	73	3 0		1 00			[illegible]	
Lungs plus heart	0 55	40	1 28	0 48	0 24	1 38	0 45	0 61	[illegible]
Dental (intraoral single exposure)	0 15	2	3 5	0 4	0 03	3		0 005	
Cervical spine	0 62	18	1 27	0 35	1 40	1 57		—	

estimated loss at certain hospitals and other installations In addition were used estimates on dental and mass miniature chest examinations made in cooperation with various bodies involved military as well as civilian The resultant frequencies per 1 000 population given in Table 5 are believed to be correct within about ±10 per cent The frequency of pelvimetry is based on a separate estimate with about the same accuracy

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Table 3 (*cont*)

dose (mGy)

		Bone marrow			Ovaries			Testes		
mean	max/ mean	min/ mean	mean	max/ mean	min/ mean	mean	max/ mean	min/ mean	mean	max/ mean
—			2 50			—		0 63	15 00	2 3
—			1 90			1 90		0 23	3 10	2 3
<1 00			4 10		0 49	6 20	2 1	0 09	1 80	2 3
<1 00			2.40		0 57	8 80	1 33	0 18	3 30	3 0
<0 50			4 20		0 15	0 56	2 1	0 58	0 16	1 63
—			3 50			1 80			—	
<0 20			9 40		0 57	7 00	1 99	0 29	5 30	3 9
—			1 70		0 53	5 90	1 67		—	
<0 10			1 53		0 54	0.24	2 3	<0 50	0 06	3 7
8 00			4 70			<1 00			—	
0 8			0 29			—			—	
3 5			0 9			<0 1			<0 1	
1 2			0 54			—			—	
0 001			0 01		<0 1	0 0001	6	<0 1	0 0001	6
—			0 38			—			—	

random the overall mean would typically have a double standard error of about 40 per cent The calculated collective dose for a certain organ summed up for all types of examinations may be in error somewhat but not much less since different hospitals were sampled for different types of examinations

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Examination type or organ examined	Energy imparted (mJ)			Absorbed dose (mGy)					
				Thyroid			Breast		
	min/ mean	mean	max/ mean	min/ mean	mean	max/ mean	min/ mean	mean	m
Hip and femur (upper third)	0 71	120	1 21		—			—	
Pelvis	0 46	87	1 38		—			—	
Lumbar spine	0 51	410	1 78	0 58	0 16	1 42	0 37	1 70	-
Urography	0 71	510	1 16	0 51	0 38	1 40	0 13	5 40	1
Stomach and duodenum	0 29	310	1 49	0 51	0 29	4 2	0 44	1 00	-
Small intestine		210			—			—	
Colon	0 63	600	1 56	0 58	0 10	2 3	0 83	0 27	1
Hysterosalpingography	0 56	90	2 6		—			—	
Cholecystography cholangiography	0 46	90	1 08	0 66	0 03	1 33	0 35	0 15	1
Thoracic spine	0 83	210	1 21	0 55	13 0	1 23	0 62	1 70	
Lungs (full size) ribs	0 61	21	1 35	0 35	0 17	2 3	0 54	0 55	1
Lungs (photofluorography)	0 50	73	3 0		1 00			2 00	
Lungs plus heart	0 55	40	1 28	0 48	0 24	1 38	0 45	0 61	1
Dental (intraoral single exposure)	0 15	2	3 5	0 4	0 03	3		0 005	
Cervical spine	0 62	18	1 27	0 35	1 40	1 57		—	

estimated loss at certain hospitals and other installations In addition were used estimates on dental and mass miniature chest examinations made in cooperation with various bodies involved military as well as civilian The resultant frequencies per 1 000 population given in Table 5 are believed to be correct within about ±10 per cent The frequency of pelvimetry is based on a separate estimate with about the same accuracy

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Table 4

Highest observed ratios of the radiation load to groups of 5–20 patients examined under different conditions e g different hospitals or personnel All radiation doses were not recorded in all patients Only ratios of 3 or more are entered

Examination type or organ examined	Ratio of highest and lowest group				
	Energy imparted	Mean absorbed dose to			
		Thyroid	Breast	Ovaries	Testes
Hip					3 7
Pelvis	3 0				10
Lumbar spine	3 5		6 2	4 3	26
Urography			14		17
Stomach	5 1	8 2	5 0	14	
Colon		4 0		3 5	13
Hysterosalpingography	4 6			3 2	
Cholecystography			11	4 3	>7
Thoracic spine			3 4		
Lungs (full size)		6 6			
Lungs (photofluorography)	6 0				
Lungs plus heart			3 1		
Cervical spine		4 5			
Dental intraoral	23	7 5		>60	>60

per cent increase of the population in the age group 25 to 29 years The total number of future children expected from the Swedish population has also changed increasing by about 10 per cent between 1955 and 1973 The population has increased by 10 per cent closely corresponding to the increased child expectancy these cause no change in the genetically significant dose

The examination frequency has increased considerably For genetically significant examinations in which the gonads may be exposed to the primary beam the number of examinations per inhabitant has increased by a factor of 2 0 (1 6–2 6) and it is assumed lacking data that the sex distribution has remained the same through the years

The ovary dose in these examinations was in 1974 about 0 8 (0 2–1 4) of the 1955 dose and for testes it was about 0 7 (0 2–1 7) These dose data include several of the present approximate estimates not based on measurements It must further be pointed out that the measured testes doses varied greatly the double standard error of the mean value of the dose at a certain examination type being about 100 per cent The ovary doses had a double standard error of about 50 per cent

The trend of age distributions represents an even larger uncertainty The age distributions 1974 were checked at two hospitals on about 1 000 patients of each

Table 5

Individual and annual collective doses The figures marked with an asterisk represent crude estima[illegible] uncertainty of which might exceed a factor of 2 The total sum includes these figures which contrib[illegible] than 20 in any case except in the case of energy imparted where the contribution is less than 30 [illegible] total excludes the figures given as upper dose limits (marked <) These contribute less than 10 excep[illegible] case of collective lung dose where they contribute less than 20 The units mJ or mGy refer to the rad[illegible] load per examination the units man × mJ or man × mGy per 1 000 to the radiation load per 1 000 Sw[illegible] inhabitants

Examination	No of exam per 1 000	Energy imparted		Thyroid dose	
		mJ	man × mJ per 1 000	mGy	man × mGy per 1 000
Hip and femur (upper third)	18 9	120	2 200	< 0 01*	[illegible]
Pelvis	15 4	87 0	1 300	< 0 01*	[illegible]
Pelvimetry	1 35	310	4 0	< 0 10	[illegible]
Lumbo-sacral	2.73	100	270	< 0 01	[illegible]
Lumbar spine	22 3	410	9 000	0 16	[illegible]
Urography	23 6	510	12 000	0 38	[illegible]
Retrograde pyelography	0.29	700	200	0 50	[illegible]
Urethrocystography	2.73	400*	1 100*	0 05	[illegible]
Stomach and duodenum	29 6	310	9 100	0 29	[illegible]
Small intestine	3.37	210	710	0 03	[illegible]
Colon	16 0	600	9 500	0 10	[illegible]
Abdomen	12.9	200*	2 600*	0 03	[illegible]
Abdomen (obstetrical)	1 40	150*	210*	0 0	[illegible]
Hysterosalpingography	0 80	90 0	72.0	< 0 01*	[illegible]
Cholecystography cholangiography	18 4	91 0	1 700	0 03	[illegible]
Thoracic spine	13 3	210	2 800	13 0	[illegible]
Lungs (full size), ribs	115	21 0	2 400	0 17	[illegible]
Lung (photofluorography)	110	73 0	8 000	1 00	[illegible]
Lung plus heart	46 6	40 0	1 900	0…4	[illegible]
Cervical spine	12.7	18 0	230	1 40	[illegible]
Shoulder clavicle, sternum	16 3	40 0	650*	< 0 50	[illegible]
Head, sinus	43 8	68 0	3 000	7 90	[illegible]
Cerebral angiography	1 18	680	810	3 00	[illegible]
Dental (intraoral single exposure)	1 500	2.00	3 000	0 03	[illegible]
Femur (middle and lower third)	5 90	50 0	300	< 0 01	[illegible]
Lower leg, knee	64 4	20 0*	1 300	< 0 01	[illegible]
Arm	50 4	5 00	250	< 0 01	[illegible]
Total	2 150		75 000		[illegible]

Table 5 (*cont*)

mary dose		Lung dose		Active bone marrow dose		Ovary dose		Testes dose	
/	man × mGy per 1 000	mGy	man × mGy per 1 000	mGy	man × mGy per 1 000	mGy	man × mGy per 1 000	mGy	man × mGy per 1 000
)5*	<0 95	<0 10*	<1 90	2 50	47 0	3 70	70 0	15 0	280
)5	<0 77	<0 10	<1 50	1 90	29 0	1 90	29 0	3 10	47 0
0	<0 14*	<0 50	<0 68	6 80	9 4	4 6	6 21	—	—
)5	<0 14*	<0 10	<0.27*	1 00	2 70	1 80*	4 90	1 0	2 70*
.0	26 0	<1 00	<22 3	4 10	90 0	6 20	140	1 80	40 0
)0	130	<1 00	<24 0	2 40	56 0	8 80	210	3 30	78 0
)0	1 50	<1 00	<0 29	3 0	0 87	8 00	2.30	13 0	3 80
.0	0 55*	0 20	0 55	3 0	8 20	15 0	41 0	⌐0 0	55 0*
)0	31 0	<0 50	<15 0	4 20	120	0 56	17 0	0 16	4 70
11	0 37	<0 20	<0 67	3 50	12 0	1 80	6.20	1 00	3 40
)7	4 30	<0 ⌐0	<3.20	9 40	150	7 00	110	5 30	85 0
11	1 40	<0 20	<2 60	3 00	39 0	2 0	26 0	2.0	26 0
)8	0 11*	<0 15	<0 21	2 20	3 10	1 5	2 10	—	—
)5*	<0 04*	<0 10*	<0 10	1 70	1 30	5 90	4 70	—	—
15	2 80	<0 10	<1 80	1 50	28 0	0 24	4 40	0 06	1 10
70	23 0	8 00	110	4 70	62 0	<1 00	<13 0	<0 20	<2 70
55	63 0	0 80	92 0	0 29	32 0	<0 03	<3 45	<0 03	<3 45
)0	220	3 50	390	0 90	99 0	<0 1*	<11	<0 1	<11
51	28 0	1 20	56 0	0 54	25 0	<0 05	<2.30*	<0 05	<2.30
1	<1 30	<0 1	<1 30	0 38	4 80	<0 01	<0 13	<0 01	<0 13
50	<8 20*	<0 10	<1 60	0 6	9 80	<0 01	<0 16	<0 01	<0 16*
10	<4 40	<0 10	<4 40	1 22	53 0	<0 01	<0 44	<0 01	<0 44
10	<0 12*	<0 10	<0 12	15 0	18 0	<0 10	<0 12	<0 10	<0 12
)05	7 50	0 001	1 50	0 01	15 0	0 0001	0 15	0 0001	0 15
)1	<0 06	<0 01	<0 06	0	0	0 50	3 00	4 00	24 0
)1	<0 64	<0 01	<0 64	0	0	<0 01	<0 64	<0 01	<0 64
)1	<0 50	<0 01	<0 50	0	0	<0 01	<0 50	<0 01	<0 50
	540		640		9?0		680		650

Table 6

Mean annual collective dose per individual from medical exposure in Sweden 1974 the mean population dose

Organ	mGy
Thyroid	0.75
Breast	0.54
Lungs	0.64
Bone marrow	0.92
Ovaries	0.68
Testes	0.65
Whole body	1.00
Genetically significant dose	0.4

sex at each hospital including urography as well as colon hip and lumbar spine examinations The latter comprised about 60 per cent of the 1955 genetically significant dose for both males and females The fraction of all examinations in the ages between 16 and 40 years was about 30 per cent higher than 1955 for urography and the difference seemed less for colon examinations Hip examinations for females also showed little difference but for males the sample gave only 40 per cent of the 1955 fraction of examinations of younger men Lumbar spine examinations of young women were somewhat less common but examinations of young males were about twice as numerous relative to 1955 In addition should be added the examinations of children below 16 years on which very little information is available The age distribution below 16 years was determined at one hospital only Up to 25 per cent of the patients were below 16 years but this is probably non-representative However it is possible that examinations of children have become comparatively more frequent, which may contribute to increase the genetically significant dose in some examinations by a factor of 2 and the overall dose by several tens of per cent. Adding together all this it is estimated that the genetically significant dose for females has been enhanced by a factor of 1.2 (0.9–1.3) due to changed age distributions, and for males by a factor of 1.3 (0.4–2.0)

As a first approximation the separate factors may be multiplied to obtain the 1974 genetically significant dose This would give 1 × 1 × 2.0 × 0.8 × 1.2 = 1.9 and 1 × 1 × 2.0 × 0.7 × 1.3 = 1.8 times higher values than those from 1955 for females and males respectively The approximation is very crude since the spread of these changes in doses for males and females is very large as well as the spread of changes in the age distributions for males

A better approximation may be the application of the change factors to each type of examination in spite of the large uncertainty associated with most of them Such a calculation results in an overall change factor between 1955 and 1974 of 1.9 for

Considerable experience on the tolerance of normal tissue to irradiation has been collected in radiation therapy (RUBIN & CASARETT 1972) Extrapolation of those data to irradiation extended over longer periods than 100 days indicates that most tissues tolerate an absorbed dose of 10 Gy or more from localized irradiation without serious long term injury The injuries which may follow at lower doses are permanent sterilization which might result from irradiation of the testes and ovaries, the much debated (RUBIN 1972) tolerance dose being about 5 Gy progressive cataract following irradiation of the eye lens by 5 Gy and injury to the human foetus at short term irradiation with even lower doses A life time dose of 10 Gy is extremely unlikely since this is about a hundred times the average life time dose of an individual whose annual contribution follows the mean doses reported in Table 6. With the exceptions mentioned the risk of late tissue injury will thus as a rule not constitute any important counterindication to radiography These can be amplified further in that temporary sterilization may follow testes doses much below 5 Gy a fetal dose of about 0 1 Gy during organogenesis may double the probability of congenital injuries and synergistic physical or chemical agents may lower the threshold of cataract formation

The risk of malignancy induction and injury to future generations has recently been summarized by the International Commission on Radiological Protection ICRP (1977) For the purpose of radiation protection it may be assumed that even the smallest radiation dose carries a risk in proportion to the dose The risk factors suggested by the ICRP have been used for the calculation of total risk per examination presented in Table 7 The ICRP gives risk factors also for endosteal tissue and for non specified organs these have due to insufficient information been applied to the mean whole body dose

Obviously this method of risk estimation is very crude with for instance no regard to age and sex variations Various limitations are discussed by the ICRP (1977)

If the estimates were correct some heavy examinations (pelvimetry and examinations of the hip colon lumbar and dorsal spine and the urinary tract) would carry an associated risk of 50 to 120 cases of serious late injury per million examinations performed Most other examinations are found in the range 10 to 50 cases per million Examinations of the cervical spine shoulder clavicle and sternum and lung (or lung plus heart) examinations using full size film fall between 2 and 10 cases per million and below 2 are found examinations of the arms and legs and single dental intraoral exposures

From Table 7 it also appears that the magnitude of the risk is surprisingly well correlated with the energy imparted to the patient The risk per joule is 0 000 within a factor of 2 up or down excepting examinations of the extremities. To some extent this is due to the application to the mean whole body dose of the risk factors for endosteal tissue and non specified organs This gives an alleged risk factor of 0 000 07 per joule even if no critical organs are exposed At most examinations

Table 7

Example of an estimate of total risk of future serious injury. The table is based on the following number of serious injuries in the form of induced malignancy or future generation genetic injury per 1 000 Gy of absorbed dose in the relevant organ (ICRP 1977). Genetic injury manifest in future generations 4.2, mammary carcinoma 2.5, leukemia 2, pulmonary carcinoma 2, thyroid carcinoma 0.5, unspecific malignancy 5.5, total 16.7. The unspecific malignancies were weighted with the mean whole body dose.

Examination type or organ examined	Cases of serious injury		
	per million examinations	per 1 000 joule of energy imparted	per year in Sweden
Hip and femur (upper third)	53.4	0.45	8.2
Pelvis	21.0	0.24	2.6
Pelvimetry	57.0	0.18	0.6
Lumbo-sacral	15.5	0.16	0.3
Lumbar spine	60.1	0.15	10.9
Urography	83.3	0.16	15.9
Retrograde pyelography	116.2	0.17	0.3
Urethrocystography	109.8	0.27	2.4
Stomach and duodenum	36.3	0.12	8.7
Small intestine	29.0	0.14	0.8
Colon	89.8	0.15	11.6
Abdomen	29.8	0.15	3.1
Abdomen (obstetrical)	22.2	0.15	0.3
Hysterosalpingography	35.1	0.39	0.2
Cholecystography, cholangiography	10.9	0.12	1.6
Thoracic spine	54.1	0.26	5.8
Lungs (full size), ribs	5.31	0.25	4.9
Lungs (photofluorography)	20.1	0.27	18
Lungs plus heart	8.27	0.21	3.1
Cervical spine	3.27	0.18	0.3
Shoulder, clavicle, sternum	5.88	0.15	0.8
Head, sinus	11.9	0.17	4.2
Cerebral angiography	82.2	0.12	0.8
Dental (intraoral single exposure)	0.20	0.10	2.4
Femur (middle and lower third)	13.19	0.26	0.6
Lower leg, knee	1.56	0.08	0.8
Arm	0.46	0.09	0.2
Total			110

this will not be a dominating risk factor. Further, the list of organs associated with induction of malignant disease has been steadily growing with time and it may be reasonable to make some allowance for possible future additions to the list.

To illustrate the uncertainties of the risk estimate, an independent estimate of

Library

malignancy risk was made using risk data from the literature (National Academy of Sciences 1972 UNSCEAR 1977) This showed similar results with a risk factor of 0 0001 per joule within a factor of 3 up or down The difference to the estimate from Table 7 is only a factor of 2 and would have been even less if genetic risks had been included in this other estimate

The collective risk to the Swedish population is also given in Table 7 If the estimates were correct, 110 cases of late injury would be induced by one year's radiographic diagnostic practice in Sweden The main contributions would come, in order from photofluorography of the lungs urography and examinations of the colon and lumbar spine The annual incidence of malignant disease in Sweden is above 30 000 cases or about 3 600 cases per million inhabitants the possible addition from radiographic diagnostic procedures is much less than one per cent

Conclusion

The physical methods of patient dose measurements in the field enable an accuracy of about 10 per cent in routine measurements of the dose to the dosemeter or the energy imparted In going from the dose in the dosemeter to the dose in the patient, about 10 per cent additional error occurs due to uncertainties in the composition of the soft tissues In some cases practical problems of dosemeter positioning may add an error of more than a factor of 2 when the dosemeter must be placed far from the organ in which the dose is to be assessed

However as a rule simple physical measurements may give the organ dose within better than ± 50 per cent if the mean of a whole group of patients is considered. The representativity of the sample of patients may however be quite poor since the individual spread of patient doses is quite wide with standard deviations up to 100 per cent Even if the physical measurements were exact, an uncertainty of the order of ± 50 per cent (95% confidence) is to be expected if the sample consists of 10 to 20 patients a number which is attainable without too much practical difficulty Estimates of collective dose involve rather large uncertainties from the sampling of hospitals, since large variations in patient dose from place to place were found in several cases a ratio between the extremes exceeding 10 The estimates of the collective dose have an uncertainty of about a factor of 2 due to all the reasons mentioned

The doses at given examinations are consistent with what would have been expected with the diagnostic techniques used It is interesting that the gonad doses on the whole seem to have been significantly reduced since 1955 although the genetically significant dose has remained unchanged The mean collective dose of about 1 mGy annually is approximately equal to the annual contribution from natural radiation sources

The radiation risk does not exceed about one case of serious late injury per 10 000 examinations and does not constitute any significant counterindication t

clinically indicated radiography The collective risk of about 100 cases annually warrants however attempts at reducing the general exposure of the patients In such attempts patient dose measurements may be useful as well as risk estimates Then it is suggested to use the middle quartile mean to get less spread of the mean dose to a group of patients and to use the energy imparted as a risk monitor with a risk factor of 0 0002 cases of late injury per joule of energy imparted to the patient

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SUMMARY

Results are reported of measurements around 1974 on a thousand patients at 13 Swedish hospitals and additionally at several photofluorographic and dental installations Energy imparted as well as doses to the thyroid breast lung bone marrow ovary and testis have been calculated for many types of examination Collective doses have been calculated and risk estimates made The energy imparted corresponds to an annual mean body dose to the Swedish population of about 1 mGy (100 mrad) and the genetically significant dose was about the same as the 1955 total of 0 4 mGy in both cases the uncertainty of the estimate is about ± 50 % The possibility of dose reduction by a factor of 2 or more using available techniques is demonstrated The risk of future serious injury is estimated to 0 0002 cases per joule of energy imparted to the patient

ZUSAMMENFASSUNG

Die Ergebnisse von Messungen um etwa 1974 bei etwa tausend Patienten von 13 schwedischen Krankenhausern und zusatzlich verschiedenen Schirmbild und zahnarztlichen Einrichtungen werden berichtet Die gegebene Energie sowie die Dosen von Thyreoidea Brust Lungen Knochenmark Ovarien und Testikeln wurden fur verschiedene Arten von Untersuchungen berechnet Die Kollektivdosis wurde berechnet und Risiko-Berechnungen vorgenommen Die verabfolgte Energie entspricht einer jahrlichen mittleren Korperdosis fur die schwedische Population von etwa 1 mGy (100 mrad) und die genetisch signifikante Dosis von etwa 0 4 mGy war ungefahr dieselbe wie 1955 In beiden Fallen war die Unsicherheit der Berechnung etwa ±50% Die Moglichkeit einer Dosisreduktion um einen Faktor von 2 oder mehr bei Verwendung befindlicher Techniken wird nachgewiesen Das Risiko einer ernsthaften Schadigung in der Zukunft wird auf etwa 0 0002 Falle per Joule der diesen Personen verabfolgten Energie berechnet

RESUME

Les auteurs présentent les résultats de mesures de doses effectuees vers 1974 sur 1 000 patients dans 13 hopitaux suédois et en outre dans plusieurs installations de radiophoto-

graphie et de radiographie dentaire Ils ont calculé pour de nombreux types d examens l énergie ainsi que les doses à la thyroïde au sein aux poumons à la moelle osseuse à l ovaire et aux testicules Ils ont calculé des doses collectives et fait des estimations du risque L énergie absorbée correspond à une dose corporelle moyenne annuelle à la population suédoise d environ 1 mGy (100 mrad) et la dose génétiquement significative a été environ la même que la dose totale en 1955 de 0 4 mGy dans ces deux cas l incertitude de cette estimation est d environ plus ou moins 50%, Les auteurs montrent la possibilité de réduire la dose par un facteur 2 ou plus en utilisant des techniques existantes Le risque de lésion grave est estimé à 0 0002 cas par joule d énergie communiqué au patient

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DOSE DISTRIBUTION AROUND A NEW FLEXIBLE AFTERLOADING APPLICATOR

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Development of techniques for intracavitary irradiation of malignant gynaecologic tumours was initiated at Radiumhemmet at the beginning of this century These efforts resulted in the so called Stockholm method devised by FORSSELL and HEYMAN (HEYMAN 1929) and further elaborated by KOTTMEIER (1964) They introduced a large number of different irradiators loaded with radium tubes to cover tumours of varying extent and location (THORÆUS 1929 WALSTAM 1954 KOTTMEIER & WALSTAM 1963)

The development of afterloading techniques both manual (SUIT et coll 1963) and remote (WALSTAM 1962 HENSCHKE et coll 1963 WALSTAM 1965 CARDIS KJELLMAN 1968 O CONNEL et coll 1967 SAUERWEIN 1968) was started at the beginning of the 1960 s Irradiators intended to provide the same degree of flexibility of the source distribution as that of the conventional Stockholm technique were constructed Further improvements of applicators with shielding facilities and loaded with ^{137}Cs have been presented during the past two decades (WALSTAM 1965 JOELSSON & BÄCKSTRÖM 1970 BÄCKSTRÖM & JOELSSON 1971) With the development of spherical ^{137}Cs sources a pneumatic transfer system offering several advantages became possible (CARDIS & KJELLMAN 1968) This has made it easier to obtain higher flexibility in source distribution and thereby improvement of the dose distribution

A commercial unit Cervitron II designed for these spherical sources has been tested at this institute Since it was not satisfactory in all desired applications a project was started with the aim of increasing the flexibility of the delivered dose distribution (U W technical and B F physical aspects)

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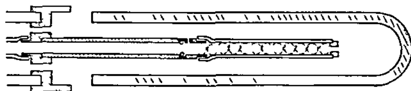


Fig 1 Standard type of applicator for Cervitron II (schematic)

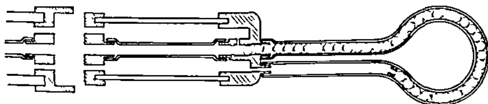


Fig 2 Developed ring shaped applicator (schematic)

Irradiators

In order to meet the requirements set up by the Stockholm method a ring shaped applicator was designed with its dimensional limitations basically set by the catheter tube holding the sources and with its shape adjustable to individual cases Dimensions less than 2 cm in diameter are now achievable A new applicator connection mechanism that easily connects and disconnects the transfer tubes to the new applicator was also developed The original applicator connectors can with a simple adaptor easily be converted to accept the new type of applicator (WESTER 1975) The described possibilities of manufacturing applicators of any shape by use of plastic tubes can with advantage be used together with the vaginal mould technique (CHASSAGNE 1966)

Dose distribution calculation

The determination of dose distribution in intracavitary irradiation has been improved by the introduction of computer techniques Computer programs have been developed for different techniques with and without afterloading (ADAMS & MEURK 1964 SHALEK & STOVALL 1968 BATTEN 1968 BECKMAN 1971 SKRETTING & KATHRUD 1972 WILKINSON 1972) A simple Fortran program was written for the applicator now presented The program is such that the only input required is the positions of the pellets and the radius of the applicator The dose rates may then be calculated in up to 20 parallel planes with a separation of one cm

All calculations of the dose rate from a ^{137}Cs point source were based on a formula developed by MEISBERGER et coll (1968) This formula is based upon measurements and calculations of the dose rate from a ^{137}Cs source in water The uncertainty in this formula is several per cent but it is satisfactory for the present purpose

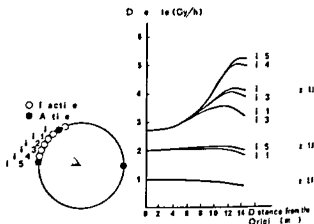


Fig. 3 Calculated dose rates along lines indicated in figure at different distances Z. The dose distribution at Z=2.0 is approximately the same along all calculation lines

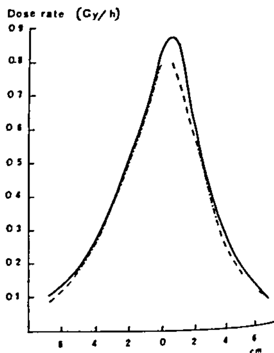


Fig. 4 The calculated (—) and measured (– –) dose rates along a line 3 cm from the central axis line to the applicator

When introducing new applicators to be used in intracavitary irradiation careful consideration must be paid to the dose distribution For the ring shaped applicator there is some risk of underdosage close to the applicator along the axis Therefore the dose rate was calculated along radii of congruent circle surfaces situated at different distances Z from the plane of the applicator The dose distribution from an applicator with a loading corresponding to low dose rate technique at Radiumhemmet is shown in Fig 3 The maximum variation along one single radius is ±4 per cent and approximately the same maximum variation in dose rates between

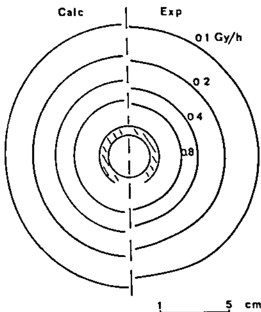


Fig 5 Calculated and measured dose distribution from a ring shaped applicator with radius 14 mm (= outer diameter of 33 mm)

different radii is obtained When using an intrauterine applicator together with this ring shaped applicator the decreasing dose rates in the centre close to the applicator may be compensated for by programming an active pellet at the place of the origin of the ring

Experiments

Dose rate measurements were performed with a cylindrical ionization chamber of the Shonka type with an outer diameter of 5 5 mm and length 11 mm and the measuring system is based on a compensation method with a charge vibrating electrometer and Fluke DC differential voltmeter (SAMUELSSON et coll 1971) The measuring time varied between 0 5 and 1 5 min The ionization chamber was movable in cartesian coordinates in a water bath by means of remote control The applicator was placed around a perspex cylinder in the water phantom which made a reproducible position of the ring shaped applicator possible An analysis of the error for this type of measurement has been performed (BENNERSTEDT & FORSBERG 1976) demonstrating that the dose rate can be determined with a maximum relative error of 8 per cent for a dose rate of 1 Gy/h rising to 12 per cent for a dose rate of 0 20 Gy/h

Results

Before making routine use of the computer program a comparison was made between measured and calculated dose rate values at some points This comparison was made both at points lying on lines parallel and perpendicular to the central axis

An example is shown in Fig 4 which gives the calculated and measured dose rates along a parallel line situated 3 cm from the central axis As can be seen the calculated values are somewhat higher the average differences between the calculated and measured dose rates are +5 per cent

The calculated and measured dose distributions for an applicator with a radius of 14 mm are given in Fig 5 In the lower part of the figure the measured dose rates decrease in comparison with the calculated dose rates which is due to increasing absorption in the applicator holder The differences—in the first case all the calculated values are higher but in the second case the calculated values are both higher and lower than the measured values—are probably due to a different activity in the applicator as compared to the activity assumed for the calculation The comparison shows that the dose distribution around the ring shaped applicator can be calculated and the proper selection of the optimum source distribution can be made before the treatment starts

Discussion

The flexibility in dose distribution of the Stockholm technique is the reason why the conventional radium treatment has not yet been replaced by an afterloading technique at Radiumhemmet By a remote control technique the exposure of the staff during the application and the treatment should be completely eliminated Greater possibilities are offered for placement of the applicators in the desired position during the treatment resulting in a more accurate dosimetry With the Cervitron II unit, unique possibilities to vary the dose distribution by programming the active pellets into different positions in the applicator are obtained With the described applicator it is possible not only to optimize the source configuration but also simply to change the form and size of the applicator increasing the flexibility of the dose distribution This together with the vaginal mould technique decreasing the fixation problems of the applicator and the use of computor programs offers possibilities for a replacement of the conventional radium therapy

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SUMMARY

A new afterloading applicator together with a computer program is described A comparison of the calculated and measured dose distribution around different applicators shows that in the future the described computer program can be used The development of the new applicator and the computer program increases the flexibility of possible dose distribution

ZUSAMMENFASSUNG

Ein neuer Nachlade Applikator mit einem Komputerprogramm wird beschrieben Ein Vergleich der berechneten und gemessenen Dosis Verteilung um verschiedene Applikatoren zeigt dass zukunftig das beschriebene Komputerprogramm verwendet werden kann Die Entwicklung des neuen Applikators und des Komputerprogramms erhoht die Flexibilitat der moglichen Dosis Verteilung

RÉSUMÉ

Description d un nouvel applicateur de surcharge avec un programme d ordinateur La comparaison de la distribution de dose calculee et mesuree autour de differents applicateurs montre que dans le futur on pourra utiliser le programme d ordinateur decrit La mise au point du nouvel applicateur et du programme d ordinateur augmente les possibilites d adaptation de la distribution de doses

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WALL SCATTERING EFFECTS IN ELECTRON BEAM COLLIMATION

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In radiation therapy the use of high energy electrons has gained increased interest in recent years Usually scattering foils and fixed field applicators are used to obtain the treatment fields The main problems then encountered are the field flatness the depth dose the roentgen ray contamination and the amount of radiation outside the field

The dose distribution is influenced by the accelerator tube exit window the monitoring transmission chamber the scattering foil the main roentgen ray diaphragms and the electron applicator

The flattening of electron fields by scattering depends strongly on the complete collimation set up (SVENSSON & HETTINGER 1967 SVENSSON 1971) The main diaphragms and the walls of the applicator scatter electrons back into the beam If these walls are flared instead of parallel they contribute less scatter The amount of wall scatter also reduces when the applicator walls are partly screened off for incident electrons by means of the main diaphragms or through restricting the entrance opening of the applicator Finally by the use of different scattering foils the contribution of wall scatter to the field can also be varied The choice of the scattering foil is also restricted by its contribution to the roentgen ray contamination of the electron beam

Once the shape and material of the applicator have been chosen its entrance

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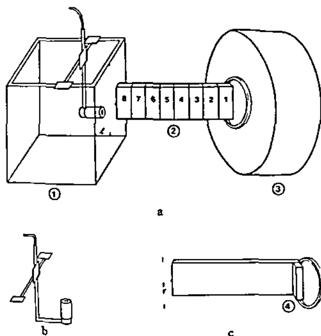


Fig 1 a) Experimental set up for measurement of electron scatter contribution from dif ferent parts of one wall ① Water phantom and remotely controlled ionisation chamber profiles measurement parallel to *l* ② Applicator wall parallel to the central axis of the beam divided in 8 parts 1–7 alumi nium, 8 perspex ③ Accelerator treatment head b) Ionisation chamber for measurements at small depths with a vertical beam c) ○ Inset positioned at top of the wall

ionisation current at + or −200 V collecting voltage is 4 per cent The saturation at these voltages is more than 99 per cent Relative curves like beam profiles and depth doses obtained with these polystyrene chambers show negligable difference when compared with the ones obtained with the Farmer chamber The measure ments were performed in a water phantom of 60 cm × 50 cm × 40 cm with remotely controlled 3 dimensional chamber positioning

For evaluation of the dose distributions scans crossing the central axis of the beam were made The scanning levels for considering the field flatness were at a depth of 0 8 cm and at the depth of maximum dose delivery for each energy Central axis depth doses were measured with the vertical beam set up and the U shaped chamber starting from the water surface

The flatness of a field was considered acceptable when the dose delivery over the whole field up to 0 5 cm from the applicator walls at the above mentioned depths did not differ by more than 5 per cent from the dose at the central axis The quality of a central axis percentage depth dose curve was considered by the therapeutic range (depth of the 85° dose level) and the slope of the steep section of the curve as suggested by BRAHME & SVENSSON (1976)

Field sizes with dimensions smaller than 16 cm are within the maximum exit aper ture of the SL 75 20 treatment head For these field sizes an applicator concept with parallel walls (Fig 2) was chosen because of its simplicity in mechanical construc tion For field dimensions larger than 16 cm flared wall applicators were taken

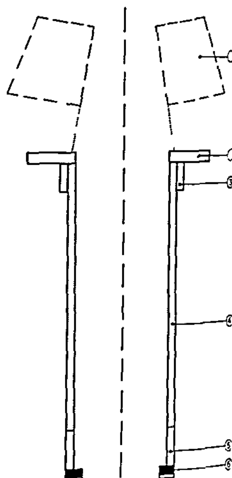


Fig 2 Construction of parallel wall applicator ① Main diaphragms defining the electron beam to the entrance aperture of the applicator ② Mounting flange C Additional aluminium shielding. ③ Aluminium applicator wall ④ Perspex end part ⑤ Field defining cerrosafe end frame

Aluminium was chosen as applicator material because of its low production of roentgen rays when struck by electrons (LINDSKOUG & DAHLER 1971 NAYLOR & WILLIAMS 1972) The walls are 1 cm thick and 35 cm long ended by 5 cm of perspex extending to the phantom surface (for treatment field visibility) which gives a total length of 40 cm and a scatter foil skin distance of 95 cm

The use of field defining frames attached to the end of the applicators, to provide intermediate and irregular field sizes was investigated These frames were made of a low melting alloy cerrosafe (Mining & Chemical Products Ltd Alperton, Wembly Middlesex United Kingdom composition 42 5% bismuth 37 7 % lead, 11 3% tin and 8 5% cadmium) and perspex

The accelerator main diaphragms were used for primary collimation of the electron beam limiting the electrons to the applicator entrance opening and thus avoiding heav shielding around this opening To prevent small changes of diaphragm setting ...encing the dose distribution in the patient the diaphragms

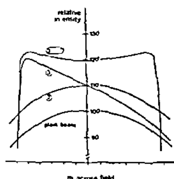


Fig 3 Scatter contribution from the applicator walls 12 MeV foil 3 Upper view of the positions of the different walls, the beam profile is measured along the dashed line at a depth of 0 8 cm (2) Profile with wall 2 (or 2') present (3) Profile with wall 3 present (3 + 3') Profile with wall 3 and wall 3 present

define an area on the applicator mounting flange at all sides 0 5 cm larger than the entrance opening (Fig 2)

A prototype applicator with removable walls was constructed to investigate how the applicators influence the dose delivery enabling experiments with one single wall with various combinations of walls and with separate parts of one wall at different distances from the central axis of the beam

The effect of restricting the entrance opening of the applicators thus partly shielding the upper part of the walls for incident electrons was investigated using strips of aluminium 2 5 cm thick and of different width (insets) and placed at the top of the walls (Fig 1 c)

Results

Parallel wall applicators

Applicator wall scattering The electrons scattered from the applicator walls strongly influence the dose distribution at small depths (up to 1 cm deep in water) at greater depths this influence gradually decreases Therefore besides at the usually taken depth of maximum dose delivery the beam profile at 0 8 cm depth has been included to investigate the influence of wall scatter and to consider the field flatness

The electron beam profile without applicator walls (plain beam profile) has been compared with the profile given by one applicator wall First measurements parallel to the wall show a regular shift upwards of the profile shape Second measurements perpendicular to the wall show a maximum increase of dose near the wall side gradually decreasing a further distance (Fig 3) The enhancement of these profiles compared to the plain beam profile is caused by the additional contribution of electrons scattered from the wall which outweighs the absence of side scatter from the region outside the wall The profile of the electron beam with two opposing walls can be shown as the result of adding the beam profile with one wall to its mirror image (Fig 3)

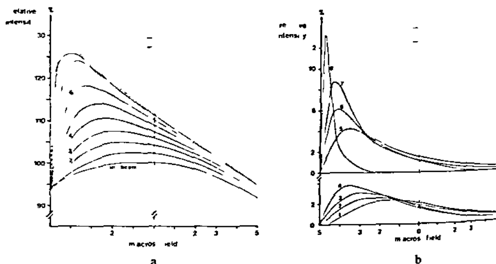


Fig. 4 Scatter contribution from applicator wall parts 12 MeV foil 3 depth 0 8 cm. a) The wall parts are positioned 5 cm left from the central axis The numbers with the curves indicate the total number of parts that are present starting from the accelerator treatment head. Curve 8 is obtained when the last part of the wall is aluminium instead of perspex b) Contribution from each separate part calculated by subtracting the curves in (a) The number with each curve here corresponds with the number of the wall part as indicated in Fig. 1 a

These properties found for all the field sizes and energies mean that the scatter contributions of the individual walls can be treated as being independent of each other Thus the beam profile obtained with each combination of the four applicator walls can be found by merely adding the separate contributions of each wall. This implies that the shape of the beam profile is determined only by the two walls defining this dimension

The beam profile referred to in the preceding paragraphs is measured parallel to one of the field dimensions (and through the field centre) For the fields determined by the parallel wall applicators the flatness measured along a diagonal appeared to be quite similar Probably the surplus of wall scatter in the field corners is balanced by the lower contribution of the plain beam because of the greater distance from the central axis and by the extra loss of side scatter Thus for the parallel wall applicators the profiles measured parallel to the field dimensions and through the field centre may be taken as a sufficient indication of field flatness For the larger field dimensions the decline of the plain beam profile prevails and the diagonal profile must also be measured for considering the field flatness

In order to investigate the scatter contribution from one wall in detail the beam profiles were measured increasing the wall length from the accelerator head by steps of 5 cm The contribution of scattered electrons from each individual part is then found by subtraction The results for a 12 MeV beam are shown in Fig 4 for the other energies the appearance of the curves was found to be similar

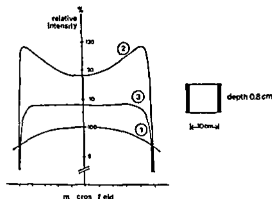


Fig 5 The effect of insets 20 MeV foil 3 (1) Plain beam profile (2) Profile with two walls (3) Profile with two walls and insets (width 1 4 cm) The profiles are measured at 0 8 cm depth along the dashed line in the diagram representing an upper view of the two walls

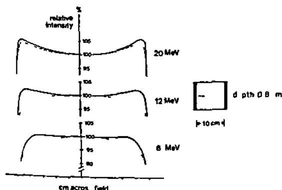


Fig 6 Comparing flatness obtained with two approaches minimizing foil thickness and using insets — Profile with two walls and foil 1 no inset — Profile with two walls and compromise inset width of 1 0 cm foil 3 All curves are measured along the dashed line in the diagram

To obtain a flat field a certain amount of scatter from the applicator walls is needed at the field sides as the plain beam contributes less with increasing distance from the central axis The scatter from the upper parts of the walls (near the accelerator head) hardly improves the profile shape it only deteriorates the depth dose (cf p 120) The scatter from the lower parts increases the dose mainly at the field edges where it is needed

Effects of insets Especially for the smaller field sizes with high energy beams the profile with two opposing walls may show an unacceptable increase of dose towards the walls depending of course on the scattering foil Such a dose distribution can be flattened by introducing insets limiting the number of electrons scattered from the walls The best position for an inset is at top of the applicator walls the upper parts of the walls are then most shielded The effect of insets is illustrated in Fig 5 for the 20 MeV beam For lower energies the profile without insets (profile 2) becomes flatter consequently a smaller inset width is required to obtain complete flatness (profile 3)

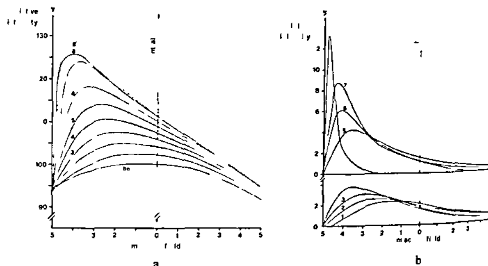


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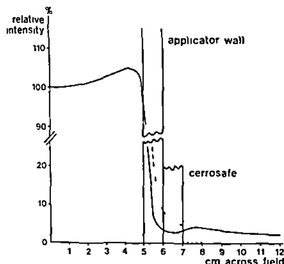


Fig 8 Radiation outside the treatment field 20 MeV foil 2 depth 0 8 cm applicator 10 cm × 10 cm — Profile without cerrosafe end frame — Profile with cerrosafe end frame 10 cm 10 cm Profile with end frame plus extra cerrosafe 10 cm long 1 cm thick against wall

insets or a thinner foil are used an improvement of beam quality is gained foil 3 plus insets and foil 1 give the same depth dose curve for each energy However with foil 2 necessary for 17 and 20 MeV to provide sufficient flatness at the largest field a small loss of depth dose must be accepted As can also be seen from Fig 7 the roentgen ray contamination of the beams is 2 5 per cent at most at 20 MeV

Flared wall applicators

Large field si es For field sizes larger than the exit aperture of the accelerator head two applicators have been studied one of field size 10 cm × 20 cm and one of 20 cm × 20 cm The walls defining the 20 cm dimension are flared the corre sponding dimension of the entrance opening of the applicator is 16 cm An additional profiled scatterer is introduced in the entrance opening of these applicators to obtain a flat field meeting the specifications set forth These scatterers are composed of perspex rectangles (for the 10 × 20 applicator) or squares (for the 20 × 20 applicator) of different thickness and dimensions piled concentrically In the 20 × 20 applicator the sides of the squares are positioned parallel to the diagonals of the field thus favouring the electrons scattered to the corners

The nominal energy of the beams is reduced with 1 MeV by the scatterers but there is no measurable contribution to the roentgen ray contamination The shapes of the percentage depth dose curves are not deteriorated by the additional scatterer the curves are only shifted 4 mm towards the surface

General

Field defining end frames Field defining frames at the exit end of the applicators have been developed to reduce the number of applicators needed for clinical practice and to offer the possibility of irregular field shapes These frames consist of a layer of

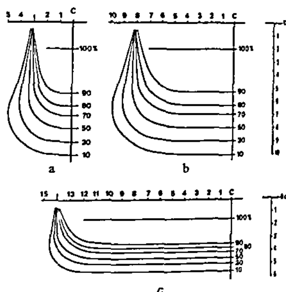


Fig 9 Examples of final isodose distributions a) 6 cm × 6 cm, 20 MeV foil 2 b) 8 cm × 16 cm 20 MeV foil 2 c) 20 cm × 20 cm diagonal 11 MeV foil 1

cerrosafe with thickness 1 cm on a layer of 0 5 cm perspex the latter acting as a spacer between frame and patient The frames only stop electrons incident on them the existing field flatness is hardly changed The amount of associated Bremsstrahlung at 20 MeV is insignificant when the shielded area extends nowhere more than 1 cm from the applicator walls With increasing distance between the walls and the field edge a roentgen level of 7 per cent can be expected under the cerrosafe when 20 MeV electrons are used With 14 and 10 MeV this reduces to 4 and 3 per cent respectively

Radiation outside the treatment field With the 20 MeV beam the dose rate under the applicator wall falls off rapidly to 8 per cent (Fig 8) and then outside the applicator slowly decreases to 2 per cent at 5 cm from the field edge A sharper decline outside the treatment field is obtained when a cerrosafe end frame defining the same field size as the applicator is used When critical regions e g the eyes are present just outside the applicator and a high energy beam is used a further reduction of dose delivery (under a 2 % level) is needed and is achieved by additional cerrosafe of 1 cm thickness placed against the last 10 cm of the applicator wall

The extra aluminium layer of 1 cm thickness added outside the first 3 5 cm of the applicator walls at the entrance side (Fig 2) stops the electrons which skim the main diaphragms and then hit a small strip around the entrance area This aluminium gives a reduction of dose of one per cent outside the treatment field

Discussion

Optimum results are obtained with the parallel wall applicators by reducing the scattering foil thickness until just sufficient flatness is reached with the highest energy

at the largest field dimension Considering the fact that the lower energy electron beams are used most in clinical practice this approach is preferable to the inset technique combined with a heavy foil providing ample scattering at the largest field dimension with its associated roentgen ray production If different foils can be selected for seperate ranges of electron energies and the foil thickness is minimized for the highest energy of each range the results are even better

Energy losses in the scattering foil and wall scatter reaching the field centre deteriorate the central axis depth dose curve The approach just described reduces the effects as much as possible within the limits set by the requirement for field flatness

For the flared wall applicators the thin foils selected in the above mentioned way for the parallel wall applicators do not give sufficient field flatness due to the low contribution of the plain beam at the field edges and the associated loss of wall scatter This can be compensated by an additional scatterer in the entrance opening of the applicator Perspex is used in order to preserve the optical field on the patient

The gain in flatness for all energies with the parallel wall applicators seems to outweigh the use of an additional scatterer with the flared wall applicators with its associated absorption of energy All fields obtained with the applicators and their field defining frames satisfy the criterion set forth for field flatness

An alternative to the present approach is the use of the main diaphragms delimiting the beam as a function of field size and electron energy Reproducible setting of the diaphragms must then be accomplished which in clinical practice demands a complicated system with motorized and electronically steered diaphragm setting

Based on the treatment fields used in the clinic a set of 12 applicators and 45 field defining frames was constructed This set offers rectangular and square fields ranging from 4 cm × 4 cm to 20 cm × 20 cm In Fig 9 examples of final isodose distributions are given

The use of a low melting material for the field defining frames also offers the possibility of irregular field shapes as cerrosafe can be moulded into any desired shape cut in polystyrene foam in the same way as known in the mantle field technique

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We wish to thank Professor J Strackee for his help and advice Professor K Breur for his interest in this work Mr P Groote for his work in designing and manufacturing the ionisation chambers Mr C M Vendeloo and Mr H Boegem for the manufacturing of the experimental collimator set and the other technicians of the department for their cooperation enabling us to do the experiments on the 20 MeV accelerator

SUMMARY

This report describes how a set of applicators covering fields with dimensions of 4 to 20 cm for the 6 to 20 MeV electron beams of a MEL SL75 20 linear accelerator was developed The electron scatter contribution of the applicator walls to the treatment field was

investigated varying the applicator entrance opening and the scattering foil with the aim of optimizing the resulting field flatness with a minimum loss of depth dose Experiments with field defining end frames and additional perspex scatterers for large field sizes are also reported.

ZUSAMMENFASSUNG

Eine Reihe von Applikatoren werden beschrieben die die Felder von Dimensionen zwischen 4 und 20 cm decken für die 6 bis 20 MeV Elektronstrahlen von einem MEL SL75-20 *Linear Accelerator entwickelt worden war Der Beitrag der Elektronstreustrahlung der* Applikatorwände zum Behandlungsfeld wurde untersucht wobei die Applikator Eingangsöffnung und die Streufolie verändert wurden mit dem Ziel die Feldfläche optimal auszugleichen mit einem minimalen Verlust der Tiefendosis Versuche mit Feldbegrenzenden Endrahmen und zusätzlichen Perspexstreuren für grosse Feldgrössen werden berichtet

RÉSUMÉ

Ce travail décrit la mise au point d un jeu d applicateurs couvrant des champs de 4 à 20 cm, *pour les faisceaux d électrons de 6 à 20 MeV d un accélérateur linéaire MEL SL75 20* La contribution de la diffusion électronique des parois de l applicateur au champ de traitement a été étudiée en faisant varier l ouverture de l entrée de l applicateur et l écran de diffusion, afin d optimiser la planéité du champ résultant avec un minimum de perte de dose en profondeur L auteur présente aussi les résultats d expériences avec des cadres situés à *l extrémité pour définir le champ et avec des diffuseurs complémentaires* en perspex pour les grandes dimensions de champ

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IRRADIATION OF MICE PRE-TREATED WITH RADIATION PROTECTIVE SUBSTANCES

A pathologic and haematologic investigation

L OUSAVAPLANGCHAI C RÖNNBACK C REHBINDER and A NILSSON

Great interest has been attached to the problem of finding a substance which combines a high irradiation protection with a low toxicity A number of substances with irradiation protecting abilities have been produced but have not been applicable as they physiologically *incapacitate the protected individuals* (CRIBORN & RÖNNBACK 1971) However WESTLAND et coll (1972) presented a compound (2 2 Dithiobis{N [(1 adamantyl)methyl]acetamidine}dihydrochloride) with low toxicity and promising irradiation protection properties when administered orally

The present investigation aimed at comparing the protective capacity of this substance and that of cysteamine hydrochloride

Material and Methods

The experiment was performed with CBA male mice 75±5 days old The animals were kept in groups of 7 in separate cages in the same room and were fed on a standard diet and water ad libitum during the observation period of 30 days following the irradiation

The irradiation was performed with a Muller MG 300 roentgen apparatus

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operated at 260 kV and 11 mA inherent filtration 4 mm Al and with a distance between the tube and the object of approximately 60 cm resulting in a dose rate of 7 7 mGy/s (48 R/min) measured in air The mice were irradiated in groups of seven in a plastic wheel and were then returned to their cages After the irradiation the animals were transferred from the National Defence Research Institute to the National Veterinary Institute, where they were housed during the observation period

The protective substance here shortly named S 75 was synthesized at the Division of Applied Chemistry National Defence Research Institute It was administered orally as a suspension in distilled water corresponding to 2 mg per animal and was given 45 min before start of the irradiation This dose was the highest one that did not cause any deaths within the first three days after irradiation of the treated animals

Cysteamine hydrochloride was used as a reference substance and was administered intraperitoneally with 6 mg per animal 15 min before irradiation Under such circumstances this substance has shown a dose reduction factor of approximately 1 8 (ÅKERFELDT et coll 1967)

The intervals between injection of the substance and the start of irradiation (45 and 15 min respectively) were chosen according to earlier knowledge of the duration of protection of the substances

Experimental schedule (14 animals in each irradiation group)

Substance	Dose	Irradiation dose
S 75	2 mg orally	
Cysteamine HCl	6 mg intra peritoneally	7 1 8 6 10 0 11 4 12 8 Gy 750 900 1 050 1 200 1 350 R
Unprotected controls		

When possible one animal from each of these groups was killed at 7 10 13 and 17 days after irradiation and the remaining animals were used to determine the irradiation mortality rate of each group The survivors were killed after an observation period of 30 days All animals included in the experiment were submitted to gross pathologic and microscopic examination In addition one animal from each group was if possible examined haematologically as were the animals killed at the four occasions given

The experiment was performed as a blind test and thus all cages were given code numbers immediately after the irradiation This code was not revealed until all examinations were finished

Complete autopsy was made of both killed (atlanto occipital dislocation) and spontaneously dead animals In addition the weight of the body liver spleen heart and kidneys of each animal was noted

Table 1

Mortality in different groups (percentages in parentheses)

Substance	Irradiation dose					
	7 1	8 6	10 0	11 4	12.8	Gy
	750	900	1 050	1 200	1 350	R
S-75	1/10 (10)	1/10 (10)	5/10 (50)	5/10 (50)	11/11 (100)	
Cysteamine	0/10 (0)	1/10 (10)	0/10 (0)	3/10 (30)	10/10 (100)	
Controls	11/11 (100)	12/12 (100)	13/13 (100)	13/13 (100)	14/14 (100)	

Stomach duodenum liver spleen mesenteric lymph nodes and sternum were fixed in Stieve s solution embedded in paraffin cut 5 μ thick and stained with Harris haematoxylin and eosin stain The blood samples were smeared and stained according to May–Grunwald–Giemsa Differential leukocyte count and microscopy of the bone marrow was performed

Results

In all irradiated groups the deaths occurred between the 4th to 24th day after irradiation i e a mortality period well known from earlier experiments within the same dose range The mortality rate is given in Table 1 and these figures have been plotted in Fig 1 to give a rough estimation of the LD_{50} for the two protected groups of animals In the unprotected group the mortality rate was 100 per cent which was unexpectedly high according to previous experiments (RÖNNBACK unpublished observations)

Pathology

Macroscopic appearances In animals from all groups haemorrhages were found in numerous organs (the average degree of which appears in Fig 2) In doses of 7 1 to 11 4 Gy the frequency and magnitude of bleedings was considerably higher for unprotected than for protected animals but more or less equal for all groups when 12 8 Gy was administered In the dose range 7 1 to 11 4 Gy cysteamine turned out to diminish the degree of heamorrhages better than did S 75

In Table 2 is given the body weight and the weight of some visceral organs of animals killed 30 days after irradiation It is notable that the mean body weight of S 75 treated animals was significantly lower than that of the cysteamine treated animals after doses of 8 6 to 11 4 Gy The observed differences concerning the organ weights were not significant In S 75 treated animals the spleen weight indicated an increase positively correlated to the radiation dose within the range of 7 1 to 11 4 Gy In cysteamine treated mice the spleen weight sharply decreased when the animals had re ceived a dose of 11 4 Gy after an earlier increase in the lower dose range (Tables 2 3)

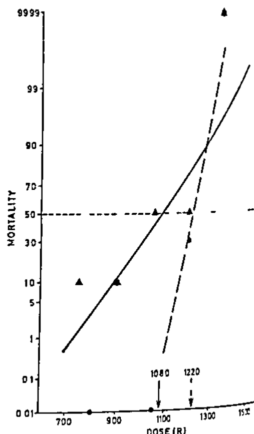


Fig 1 Mortality in protected irradiated groups Arrows indicate approximate LD_{50} ▲ S 75 ● Cysteamine HCl

Microscopy In the stomach hyperemia mucosal or subserosal haemorrhages and vacuolar degeneration of the secretory cells of the gastric gland were found in the irradiated mice of all groups (Fig 3)

In the intestine no evidence of hyperemia was present in animals given S-75 or cysteamine but appeared in a small degree in mice only irradiated Haemorrhages were insignificant Atrophy of the stroma of villi was a constant finding (Fig 4).

The main lesions observed in the liver were hyperemia localized haemorrhages, vacuolar degeneration centrilobular necrosis and hyperplasia of Kupffer cells (Fig 5)

In the spleen hyperemia hypoplasia of the white pulp extramedullary haematopoiesis shrinkage and haemosiderosis were remarkable lesions Haematopoiesis was prominent in the protected animals (Fig 6)

The lesions in the mesenteric lymph nodes were hyperemia and haemorrhages, lymphatic hypoplasia fibrosis oedema and polymorphic infiltration (Fig 7)

In the bone marrow the most marked lesions were haemosiderosis and cellular depletion varying from hypoplasia to aplasia (Fig 8) The protective properties of cysteamine appeared to be somewhat better than those of S 75 In all protected mice

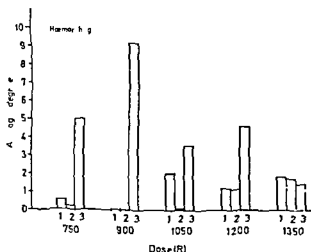


Fig 2 Gross pathology Average degree of haemorrhage in the stomach intestine lymph nodes, brain, meninges, heart and urinary bladder The average degree is calculated by adding the degree of lesions (0 = no lesion 1 + = slight 2 + = moderate 3 + = severe) of each organ in the group and dividing the sum with the number of animals in that group The degree of lesion was classified according to an arbitrary scale The experiment groups were indicated (1) S 75 treated 45 min before irradiation (2) cysteamine HCl treated 15 min before irradiation (3) irradiated only

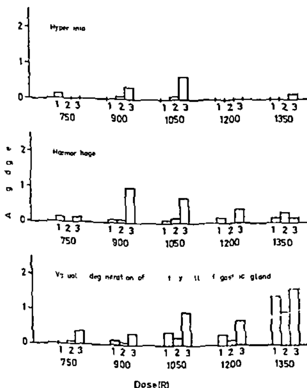


Fig 3 Microscopy of stomach Average degree (cf Fig 2) of hyperemia mucosal and subserosal haemorrhage and vacuolar degeneration of secretory cells

the bone marrow showed a distinct regeneration of a very uneven distribution and a heterogeneous cellular appearance Some marrow compartments were regenerated while others in the same sternum showed complete aplasia (Fig 9) Some regenerative marrows contained mainly one kind of cells such as megakaryocytes

Table 2

Body and organ weights of animals killed at the end of observation period (in g) Mean ± SE

		7 1 750	8 6 900	10 0 1 050	11 4 1 200	12 8 1390
Body weight	S 75	29 66 ±0 49	26 20 ±0 73	23 24 ±1 51	23 21 ±0 97	–
	Cysteamine	27 11 ±0 30	28 18 ±0 33	29 87 ±0 45	28 7[illegible] ±0 56	–
Heart	S 75	0 122 ±0 003	0 118 ±0 008	0 111 ±0 006	0 113 ±0 010	–
	Cysteamine	0 119 ±0 003	0 128 ±0 005	0 131 ±0 004	0 13[illegible] ±0 004	–
Liver	S 75	1 881 ±0 087	1 305 ±0 032	1 534 ±0 181	1 314 ±0 125	–
	Cysteamine	1 198 ±0 017	1 341 ±0 045	1 969 ±0 100	1 706 ±0 049	–
Spleen	S 75	0 139 ±0 012	0 163 ±0 012	0 173 ±0 044	0 185 ±0 0[illegible]0	–
	Cysteamine	0 168 ±0 0[illegible]0	0 183 ±0 018	0 192 ±0 014	0 147 ±0 005	–
Kidney	S 75	0 483 ±0 010	0 387 ±0 013	0 402 ±0 035	0 394 ±0 025	–
	Cysteamine	0 433 ±0 010	0 463 ±0 019	0 497 ±0 014	0 460 ±0 014	–

Table 3

Relative weight of organs from mice killed at the end of observation period ($\times 10^{-4}$)

		7 1 750	8 6 900	10 0 1 050	11 4 1 200	12 8 1390
Heart	S 75	4 11	4 50	4 77	4 87	–
	Cysteamine	4 39	4 54	4 39	4 60	–
Liver	S 75	63 42	49 81	66 01	56 61	–
	Cysteamine	44 19	40 24	65 92	59 40	–
Spleen	S 75	4 69	6 22	7 44	7 97	–
	Cysteamine	6 [illegible]0	6 49	6 43	5 1[illegible]	
Kidney	S 75	16 29	14 77	17 30	16 98	–
	Cysteamine	15 97	16 43	16 64	16 02	–

Haematology Rather few blood samples could be collected from the unprotecte only irradiated mice as those animals died before the day determined for killir Some blood smears were due to scarcity of leukocytes unsuitable for differer count The relation between dose kind of protective substance duration af

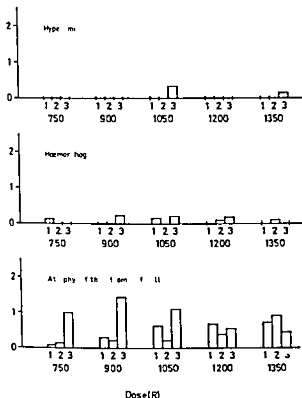
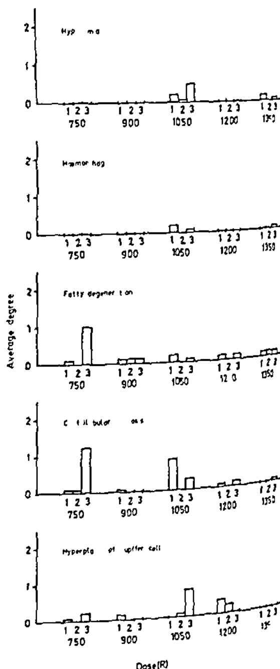


Fig 4 Microscopy of duodenum Average degree of hyperemia mucosal haemorrhage and atrophy of stroma of villi

irradiation and the number of blood samples which were countable uncountable and uncollectable are presented in Fig 10 Blood samples from protected irradiated animals showed a tendency to relative neutrophilia anisocytosis and polychromasia

Discussion

Both the substances tested had protective properties The dose reduction factor for cysteamine was previously reported to be 1 8 (ÅKERFELDT et coll 1967) The mice in the present series seemed to be more sensitive to irradiation than in previous experiments possibly due to stress (transport post irradiation all unprotected mice died after 7 1 Gy The true LD_{50} was therefore recalculated in extra groups of unprotected mice and gave a dose reduction factor of 1 6 for cysteamine and 1 4 for S 75 Cysteamine thus appeared to be slightly more effective than S-75 which however has the advantage of being effective after oral administration in small doses In addition the duration of protection by S-75 is about three times that of cysteamine and the optimum effect during these circumstances occurred about 45 min after administration (RONNBACK unpublished results) From a pharmacologic



g 5 Microscopy of liver Average degree of hyperemia localized haemorrhage vacuolar degeneration centrilobular necrosis and hyperplasia of Kupffer cells

point of view S 75 therefore seems to be the more promising substace for practical use

In the dose range from 7 1 to 11 4 Gy haemorrhages were significantly more prominent in the unprotected than in the protected groups of mice In the la cysteamine turned out to inhibit bleedings more effectively than did S 75 At the

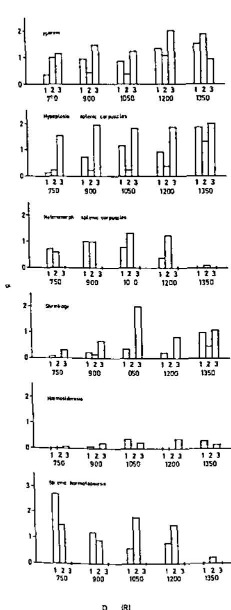


Fig 6

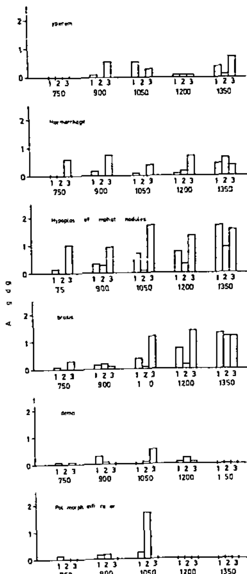


Fig 7

Fig 6 Microscopy of spleen Average degree of hyperemia hypoplasia of splenic corpuscles hetero morphic splenic corpuscles shrinkage haemosiderosis and splenic haematopoiesis

Fig 7 Microscopy of mesenteric lymph nodes Average degree of hyperemia, diffuse or peripheral haemorrhage hypoplasia of lymphatic nodules fibrosis oedema and polymorph infiltration

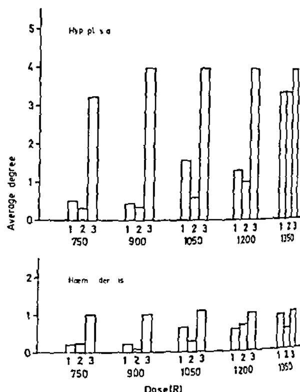


Fig 8 Microscopy of bone marrow Average degree of hypoplasia up to aplasia and haemosiderosis

highest dose level (12 8 Gy) the frequency of bleedings was about the same in all *groups* whether the mice were protected or not

In the liver, after 7 1 Gy unprotected mice showed only minor evidence of injury *such* as a slight vacuolar degeneration and centrilobular necrosis while the protected ones showed practically *no changes* The lesions were apparently indirectly produced as a consequence of a severe anemia in the unprotected animals

In unprotected *mice* hypoplasia of splenic corpuscles was very prominent as well as shrinkage *fibrosis* and haemosiderosis No evidence of heteromorphic splenic corpuscles and splenic haematopoiesis occurred in the unprotected animals but it was very marked in protected mice (Fig 6) indicating an ability of S 75 and cysteamine to protect lymphoid cells from irradiation injury Both substances appeared to have a beneficial effect upon the recovery mechanism of the haematopoietic system corresponding to HARTWEG's (1957) observations with cysteine when given to irradiated Albino rats The strong splenic hyperemia in the unprotected mice largely seemed to depend upon destruction of the splenic corpuscles and a slight capacity of regeneration

The increase in weight of the spleen (Tables 2 3) and the magnitude of haematopoiesis and of heteromorphic splenic corpuscles in S 75 protected animals may point towards a protective and regenerative capacity of S 75 more directed towards this organ compared to the effect of cysteamine

Severe hypoplasia up to aplasia was found in the bone marrow of unprotected



Fig 9 Unproper cellularity of regenerating bone marrow To the left regenerating marrow to the right aplastic marrow Cysteamine protected animal irradiation dose 10 0 Gy killed 30 days after irradiation H & E stain. × 80

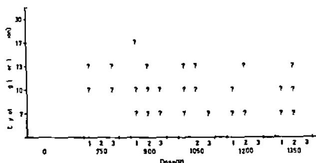


Fig 10 Blood samples taken during the observation period being countable uncountable or uncollectable (the animals died before the day they were to be killed)
— = differential leukocyte count possible
? = too few leukocytes to be counted
– = no blood samples taken
0 untreated control
1 S 75 treated
2 cysteamine HCl treated
3 irradiated only

mice (Fig 8) Regeneration of myeloid tissue occurred only in the protected mice and cysteamine was somewhat more effective in protection of the bone marrow than was S 75 The stimulative effect of both substances seemed to be absent or low and thus in accordance with previous results (STOKKE 1968)

A non uniform regeneration and a heterogeneous cellularity appeared in the bone marrow of protected animals It is likely that both protective substances were able to protect haematopoietic tissue but not all types of cells to the same degree Thus regeneration occurred from a few selected cells resulting in an abnormal appearence of an unproper cellularity of the regenerating marrow which mostly consisted of one kind of cells (Fig 9) Furthermore as circulation is not equal in all bone marrows some areas might have had a low oxygen tension at the moment of irradiation contributing to an increased resistance to radiation In protected mice some haematopoietic cells probably survived in marrows with a low oxygen tension and regeneration took place as mentioned

Haemosiderosis of the bone marrow and the spleen indicates destruction of erythrocytes which was more extensive in unprotected mice The lymph nodes seemed to be better protected by cysteamine than by S 75 However both substances reduced the degree of hypoplasia and fibrosis compared to unprotected animals (Fig 7)

Unfortunately, most of the unprotected mice died before the day determined for killing Therefore only a few blood samples were obtained from these animals all uncountable on account of a severe leukopenia Of the protected animals more countable blood samples were obtained from cysteamine treated animals than from S 75 treated animals (Fig 10)

The sensitivity of the lymphocyte and the very slow recovery of the lymphoid tissue apparently resulted in a relative neutrophilia of the countable blood samples Anisocytosis and polychromasia which occurred in protected mice mirrored the erythropoietic response to anemia A rather late effect in the protected mice was a chronic anemia which appeared in concordance with the slow progress of erythropenia associated with the 20 to 40 day life span of the erythrocytes (SCHALM et coll 1965) and a lower sensitivity of the erythrocytes to irradiation

Acknowledgement

The authors are indebted to Dr J Santesson for preparation and supply of the substance S 75 used in the investigation

SUMMARY

CBA male mice were irradiated with single doses of 7 1 8 6 10 0 11 4 or 12.8 Gy respectively A protective substance 2 2 Dithiobis{N [(1 adamantyl)methyl]acetamidine}-dihydrochloride here called S 75 was administered orally 45 min before start of irradiation. Cysteamine HCl was used as a reference protective substance Pathologic and haematologic examination of irradiated animals was performed Cysteamine had somewhat better protective abilities than did S 75 but the latter had some other properties which indicate its possible usefulness in practice

ZUSAMMENFASSUNG

Männliche CBA Mäuse wurden mit Einzel Dosen von 7 1 8 6 10 0 11 4 und 12 8 Gy bestrahlt Eine Schutzsubstanz 2 2 Dithiobis{N[(1 adamatyl)methyl]acetamidine}dihydrochloride hier S 75 bezeichnet wurde 45 Minuten vor Beginn der Bestrahlung oral verabfolgt Cysteamine HCl wurde als Referenz Schutzsubstanz verwendet Pathologische und hämatologische Untersuchungen der bestrahlten Tiere wurden vorgenommen Cysteamine zeigte etwas bessere Schutzeigenschaften als S 75 die letztere Substanz hatte jedoch andere Eigenschaften welche auf dessen mögliche praktische Anwendbarkeit hinweisen

RÉSUMÉ

Des souris mâles CBA ont été irradiés par des doses uniques de 7 1 8 6 10 0 11 4 ou 12 8 Gy Une substance protectrice le 2 2 Dithiobis {N [(1 adamantyl)methyl]acetamidine}-dihydrochloride appelée ici S 75 a été administrée par voie orale 45 minutes avant le début de l irradiation Le cystéamine HCl a été utilisé comme substance protectrice de référence. Des animaux irradiés ont subi un examen anatomo pathologique et hématologique La cystéamine a un effet protecteur un peu meilleur que le S-75 mais ce dernier a quelques autres *propriétés qui montrent qu il peut être utile en pratique*

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FROM RADIUMHEMMET KAROLINSKA SJUKHUSET S 104 01 STOCKHOLM SWEDEN

TIME FACTOR IN PHA RESPONSIVENESS OF HUMAN BLOOD LYMPHOCYTES AFTER IN VITRO IRRADIATION

EDWARD BARAL and HENRIC BLOMGREN

Previous investigations (BARAL & BLOMGREN 1976 SCHREK & STEFANI 1964 CIRKOVIC 1969 BRAEMAN & MOORE 1974) have demonstrated that exposure of human peripheral lymphocytes to increasing doses of roentgen rays reduces the PHA responsiveness as a two phased function A steep fall of the *PHA reaction* is recorded up to 8 Gy followed by a plateau phase at higher doses *This observa*tion may be interpreted in several ways One possibility could be that there exist a true difference in sensitivity to radiation between two lymphocyte subpopulations An alternative explanation could be that there are two subpopulations of PHA reactive cells one which is activated rapidly by PHA and thereby builds up a repair system for the structures injured by irradiation and another subpopulation which is activated more slowly by PHA and that dies in interphase

In this investigation this question has been explored by varying the sequence and time intervals between radiation exposure and PHA stimulation

Material and Methods

Blood samples were obtained from healthy volunteers Venous blood was drawn in heparinized syringes and nucleated cells were separated be centrifugation on *Ficoll* Isopaque (BOYUM 1968) The cells were washed twice by centrifugation in *Eagle* Minimal Essential Medium supplemented with Earle s salts (MEM) *Of the cells* 90 to 95 per cent had the morphology of small lymphocytes the *remainder being*

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classified as monocytic or granulocytic cells Cell preparations (1.0×10^6 cells/ml) were suspended in MEM supplemented with penicillin streptomycin and 10 per cent of heat inactivated human serum (HS) Cultures that received PHA were incubated with this agent for 6 12 24 48 and 72 hours in a humidified 5 per cent CO_2 air atmosphere The cells were then washed by centrifugation and transferred to glass Petri dishes and irradiated After irradiation the cells were washed once in MEM and placed in the wells of plastic microtest plates containing 0.2 ml of medium and 1×10^5 cells All cultures were set up in quadruplicate PHA was added to some of the cultures and others served as controls After four days of incubation at 37 C in a humidified 5 per cent CO_2 air atmosphere each culture received 1 μCi ^{3}H thymidine (5 Ci/mM Radiochemical Center Amersham England) Twenty four hours later incorporated activity was determined (LILLIEHÖÖK & BLOMGREN 1974) and expressed as counts per minute (cpm) Other lymphocyte preparations from each donor were irradiated before PHA stimulation The cells were washed once after irradiation and thereafter incubated in MEM with HS and antibiotics for 1 12 24 48 and 72 hours The cells were then cultured with PHA in microtest plates as described Trypan blue exclusion was used to determine cell viability Isotope uptakes of unstimulated cultures were subtracted from those obtained in corresponding PHA stimulated cultures taken from the same donor Mean values of quadruplicate cultures were calculated on an arithmetic basis Stimulation of irradiated cultures was expressed as the percentage of incorporation of ^{3}H thymidine in comparison with unirradiated controls

Irradiation of cell suspensions was performed at room temperature as described previously (BARAL & BLOMGREN 1976) with Siemens equipment operated at 140 kV and 20 mA The doses employed were 2 4 8 16 and 32 Gy

Lymphocytes were stimulated with phytohaemagglutinin (PHA Bacto-phyto haemagglutinin M Difco Lab Detroit Mich USA) The contents of commercially available vials were dissolved in 5 ml of MEM (100 per cent of PHA) This solution was further diluted to a final concentration of 3 per cent which has previously been shown to yield optimum DNA synthetic responses of human lymphocytes (BLOMGREN 1974)

Results

The results of one representative experiment (Fig 1) demonstrate that the dose response curves are essentially similar for lymphocytes which were stimulated with PHA for 1 to 24 hours following irradiation in vitro A profound decrease of reactivity was found in a large fraction of cells in the dose interval 1 to 8 Gy while a smaller fraction was only slightly affected by increasing the dose from 8 to 32 Gy When the time between irradiation and the subsequent stimulation was extended to 48 to 72 hours no resistant cell fraction was detected The stimulations [illegible] as cpm of the non irradiated PHA stimulated cultures are presented in Tab[illegible]

The proportion of the resistant cells decreased somewhat when the lymp[illegible]

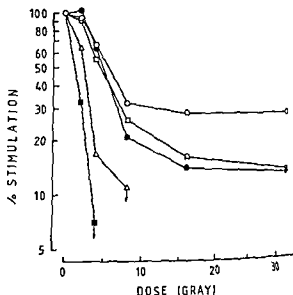


Fig 1 Relative ^{3}H thymidine uptakes of irradiated lymphocyte preparations exposed to 3 per cent of PHA at different times following irradiation PHA added ○ 1 hour ● 12 □ 24 ■ 48 and △ 72 hours after irradiation Arrows indicate that stimulation of the cells was less than 0 5 per cent

were cultured with PHA for different times between 12 and 72 hours before irradiation (Fig 2) For comparison an experiment in which the cells were PHA stimulated 1 hour after irradiation is also illustrated The stimulation of the unirradiated cultures as well as the calculated radiation resistant cell fractions are listed in Table 2 This cell fraction was estimated by the point of intersection between the linear regression line (y=kx+L) of the observations making up the plateau of the curves and the ordinate Two observations emerge from this table the absolute stimulations were decreased by prior exposure of the cells to PHA and the fraction of radiation resistant cells decreased by preincubation with PHA

Discussion

The majority of cells which are activated to DNA synthesis and subsequent mitosis by PHA are T cells (Greaves & Janossy 1972) This subset of the lympho-

Table 1

PHA stimulations of non irradiated cell cultures presented in Fig 1

Time between irradiation and PHA stimulation (hours)	^{3}H thymidine incorporations (mean cpm)
1	255 000
12	272 000
24	281 000
48	348 000
72	186 000

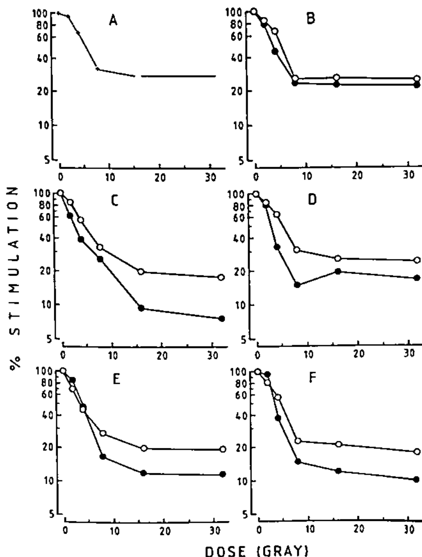


Fig 2. Relative H thymidine uptakes of irradiated lymphocyte preparations cultured with 1 [illegible] PHA for different times before irradiation A—PHA added 1 hour after irradiation [illegible] D—24 E—48 and F—72 hours incubation with PHA before irradiation ● [illegible] O Control cultures incubated for the corresponding times in MEM and [illegible] PHA immediately after irradiation

cyte population may be divided into two groups differing in sensitivity to ionizing radiation in vitro (SCHREK & STEFANI CIRKOVIC BRAIMAN [illegible], BARAL & BLOMGREN) However in a previous report (BARAL et coll [illegible]) the proportion of radiation resistant PHA reactive cells was not increased in the blood of patients with malignancy after radiation therapy in spite of the [illegible] the lymphocyte

Table 2

PHA stimulations of non irradiated cell cultures and proportions of resistant cells of the lymphocyte preparations presented in Fig 2

Time between PHA stimulation and irradiation (hours)	Pretreatment	³H thymidine incorporations (mean cpm)	Fraction of resistant cells[1] (per cent)	Radiation doses for estimating the resistant cell fraction (Gy)
6	stimulated	101 000	24	8-37
	unstimulated	121 000	26	8-37
12	stimulated	54 000	11	16-32
	unstimulated	278 000	35	8-37
24	stimulated	146 000	16	8-37
	unstimulated	261 000	32	8 37
48	stimulated	53 000	17	8-37
	unstimulated	200 000	28	8-37
72	stimulated	44 000	16	8 37
	unstimulated	191 000	24	8 37

[1] The resistant cell fraction was estimated by calculating the linear regression line (y = kx + 1) of the stimulations obtained in cultures exposed to the indicated doses of radiation The value obtained by extrapolation to 0 Gy has been taken as the fraction of resistant cells

number was reduced to less than 50 per cent Thus there was not a selective elimination of sensitive lymphocytes as could be expected This finding argues against the existence of two distinct groups of PHA responsive lymphocytes differing in sensitivity to radiation

One possible explanation for the two phased dose response curve of PHA responsive peripheral lymphocytes could be that this subpopulation contains one group of cells which are activated rapidly and another more slowly by PHA Cells of the first group could theoretically survive the radiation injury due to the rapid build up of repair enzymes during PHA activation This thesis is supported by the finding that PHA activated lymphocytes exhibit significantly elevated DNA polymerase and ligase activities (LOEB et coll 1968 LOEB & AGARWAL 1971 AGARWAL & LOEB 1972 PEDRINI et coll 1972) Moreover HASHIMOTO et coll (197 have observed a ten fold increase of rejoining of single strand DNA breaks in PHA activated lymphocytes compared with non transformed The report by SCHREK & STEFANI demonstrating an increased resistance of PHA activated lymphocytes supports this view

This investigation employing human peripheral lymphocytes has failed to demonstrate any increase of the radiation resistant fraction of PHA responsive lymphocytes after exposure of the cells to the lectin for time periods ranging from 6 to 72 hours If anything the radiation resistant fraction decreased by pre-

ultivation of the lymphocytes with PHA The present data are in agreement with hose showing that the PHA response of lymphocyte preparations decreases as the ime interval between radiation and exposure to PHA is increased (SCHREK & STEFANI) However a surprisingly large proportion of cells were able to respond to PHA 24 hours after irradiation

Various proliferating mammalian cells have been shown to become progressively more sensitive to radiation as they proceed towards mitosis (TERASIMA & TOLMACH 1963 SINCLAIR & MORTON 1966 SINCLAIR 1968) Theoretically this could explain the biphasic dose response curve since lymphocytes in the blood may be in different phases of the cell cycle This possibility seems unlikely considering the fact that the radiation sensitive fraction is at least three times greater than the resistant fraction and that less than 0 5 per cent of peripheral blood lymphocytes are in the S phase However it is logical to expect that a larger proportion of lymphocytes approaches the radiation sensitive phases of the cell cycle following PHA activation This was ound to be the case in the present series

In conclusion the results of this investigation do not give any support for the view that PHA stimulation of lymphocytes can rescue them from a death induced by radiation

Acknowledgements

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SUMMARY

Human blood lymphocytes were irradiated in vitro prior to or following PHA stimula ion Radiation dose response profiles indicate that PHA pretreatment of cells has no protective effect PHA reactivity of the cells decreases with increase of the time interval between irradiation and subsequent PHA stimulation

ZUSAMMENFASSUNG

Menschliche Blutlymphozyten wurden in vitro vor oder im Anschluss an eine PHA Stimulation bestrahlt *Die Dosis Responskurven deuten darauf hin* dass PHA Vorbehand lung der Zellen keinen Schutzeffekt hat Die PHA Reaktivitat der Zellen fallt mit steigen dem Zeitintervall zwischen Bestrahlung und nachfolgender PHA Stimulation

RESUME

Des lymphocytes sanguins humains ont été irradiés in vitro avant ou apres stimulation par PHA Les profils de réponse en fonction des doses de radiation montrent que le pre traitement par PHA des cellules n a pas d effet protecteur La réactivite des cellules PHA diminue quand l intervalle de temps entre l irradiation et la stimulation ultérieure par PHA augmente

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ROM THE DEPARTMENT OF ONCOLOGY AND RADIOTHERAPY AND THE CYTOLOGY LABO-ATORY UNIVERSITY INSTITUTE OF PATHOLOGY AARHUS KOMMUNEHOSPITAL DK 8000 ARHUS DENMARK AND THE DEPARTMENT OF CYTOLOGY INSTITUTE OF TUMOUR PATHOLOGY KAROLINSKA SJUKHUSET S 104 01 STOCKHOLM SWEDEN

NEEDLE ASPIRATION BIOPSY IN THE DIAGNOSIS OF LYTIC BONE LESIONS IN HISTIOCYTOSIS X EWING S SARCOMA AND NEUROBLASTOMA

P THOMMESEN P FREDERIKSEN T LOWHAGEN and J S WILLEMS

Conventional radiography of bone lesions in children and adolescents gives limited nformation on the nature of the process Before treatment a morphologic diagnosis is always necessary The value of open surgical biopsy is clear but surgical explora ion may be an elaborate procedure Needle biopsy under fluoroscopic control offers an adequate alternative (SCHAJOWICZ 1955 FRANZEN & STENKVIST 1968) The present report constitutes a review of the experiences with the aspiration biopsy method in cases of histiocytosis X Ewing s sarcoma and metastatic bone lesions of neuro-blastoma

Materials and Methods

A series of 15 patients under 20 years of age (8 girls 7 boys) with lytic bone lesions from Radiumhemmet in Stockholm and from Radiumstationen in Aarhus treated 1972 to 1976 was reviewed Twelve patients were between one and 8 years the other 3 were 10 14 and 18 years of age respectively This series included 8 patients with histiocytosis X 4 with Ewing s sarcoma and 3 with neuroblastoma

Specimens from solitary or multiple bone lesions had been taken under fluoroscopy in all patients using a 2 mm thick needle for aspiration as described by FRANZEN &

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Fig. 1

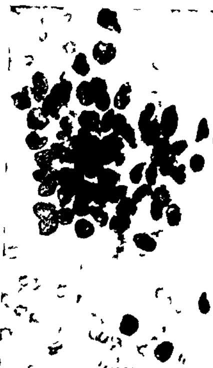


Fig. 2

Fig. 1 Histiocytosis X. Needle aspiration biopsy from lytic bone lesion in the sacrum. Smear dominated by *histocytic cells* with lymphocytes and some eosinophilic granulocytes (May-Grünwald-Giemsa × 500)

Fig. 2. Ewing's sarcoma Needle aspiration biopsy from lesion in right femur Small malignant tumour cells with *scanty* cytoplasm either dispersed or in small clusters (May-Grünwald-Giemsa × 500)

STENKVIST Smears had been air dried and stained with the May-Grunwald-Giemsa method *For* each case the clinical follow up as well as slides from either biopsy or autopsy material were available for correlation with the cytologic data

Results

A representative specimen for cytologic examination was obtained in 13 of the 15 cases *In all* instances in which enough material was available (7 of 8 cases) histiocytosis X could be diagnosed cytologically but it was not possible with certainty to differentiate Ewing's sarcoma from neuroblastoma

Discussion

Needle aspiration biopsy of lytic bone lesions for cytologic examination has been a longstanding practice in some centers where it is *often* combined with micros-

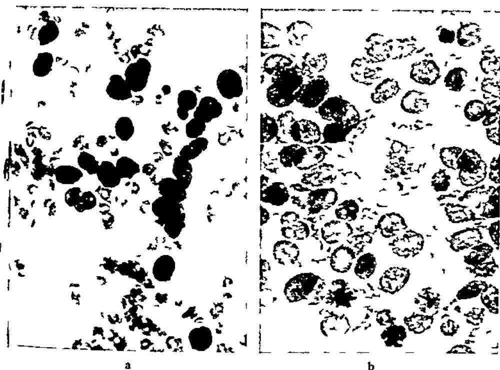


Fig 3 Neuroblastoma Needle aspiration biopsy from lesion involving the sacrum Cytologically malignant cells of varying size a) Part of the smear consists of small cells similar to those in Ewing s sarcoma b) A tendency to more abundant cytoplasm rosette formation and a proteinaceous back ground substance is seen (May–Grunwald–Giemsa ×500)

of small bone fragments (SCHAJOWICZ 1955 FRANZEN & STENKVIST) It is technically a simple and rapid method and if representative material is obtained often gives valuable supplementary information to the clinical and radiologic data As such it can influence the management of the patient at an early stage of investigation

Smears from all the histiocytosis X cases were very cellular and consisted of a combination of histiocytic cells with regular pale staining nuclei and abundant cytoplasm multinucleated histiocytes phagocytizing histiocytes and eosinophilic granulocytes (Fig 1) Several authors agree on the relative ease in making a diagnosis in such cases (SCHAJOWICZ 1973 FRANZEN & STENKVIST) Smears from patients with Ewing s sarcoma (Fig 2) and neuroblastoma (Fig 3) had a monotonous cyto logic appearance They consisted of rather small obviously malignant tumour cells with scanty cytoplasm and little cohesiveness but with some tendency to clustering In some cases the cells lay against a proteinaceous background substance STORMBY & ÅKERMAN (1973) stated that in Ewing s sarcoma the small malignant cells were dissociated in contrast to the rosette formation in neuroblastoma HAJDU & MELAMED (1971) emphasized the close cytologic resemblance between Ewing s sarcoma and

neuroblastoma This is in accordance with the present observations and because of this resemblance it was not possible with certainty to differentiate Ewing s sarcoma from neuroblastoma

Differentiation between small round cell tumours in bone calls for cytochemical methodology Intracellular demonstration of glycogen is highly suggestive of Ewing s sarcoma (SCHAJOWICZ 1959 SALZER KUNTSCHIK 1967) whereas neurosecretory granules in electron microscopic preparations support a neuroblastoma diagnosis (MACKAY et coll 1975) The small amounts of tissue required for such determinations are easily obtained by needle aspiration biopsy This renders needle biopsy particularly suitable and indicated in the differential diagnosis of small cell tumours in bone

SUMMARY

Cytologic smears obtained by needle aspiration biopsy of lytic bone lesions in 15 patients with histiocytosis X *Ewing s sarcoma and neuroblastoma* were reviewed After conventional staining histiocytosis X could be diagnosed and differentiated from small cell tumours such as Ewing s sarcoma and neuroblastoma The need for sampling material for cytochemical and ultrastructural analysis of these small cell tumours by needle aspiration is emphasized

ZUSAMMENFASSUNG

Die zytologischen Ausstriche bei der Nadel Aspirationsbiopsie von lytischen Knochenschadigungen bei 15 Patienten mit Histiocytosis X Ewings Sarkom und Neuroblastom werden beschrieben Nach konventioneller Farbung konnte die Histiocytosis X diagnostiziert und von den Klein Zelltumoren wie Ewings Sarkom und Neuroblastom abgegrenzt werden Die Notwendigkeit Materialproben fur zytochemische und ultrastrukturelle Analysen dieser kleinzelligen Tumoren durch die Nadel Aspirationsbiopsie zu entnehmen, wird hervorgehoben

RESUME

Des frottis cytologiques obtenus par biopsie aspiration à l aiguille de lésions osseuses lytiques chez 15 patients atteints d histiocytose X de sarcome d Ewing et de neuroblastome ont été revus Après coloration habituelle l histiocytose X a pu être diagnostiquée et différenciée des tumeurs à petites cellules tels que le sarcome d Ewing et le neuroblastome Les auteurs insistent sur la necessité de faire des prélèvements de ces tumeurs à petites cellules par aspiration a l aiguille pour des études cytochimiques et ultra structurales

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STEREOTACTIC GAMMA IRRADIATION OF BASILAR ARTERY IN CAT

Preliminary experiences

A NILSSON J WENNERSTRAND D LEKSELL and E O BACKLUND

In clinical neurosurgery cases with arteriovenous malformations of the brain [illegible] fairly often encountered When indications for treatment are present surgical rem[illegible] of the malformation is often possible However in some cases the topogra[illegible] arrangement of the pathologic vascularity does not permit radical surgery As [illegible] intracerebral vessels are sensitive to irradiation radiation therapy in some cases [illegible] proved successful (SVIEN & PESERICO 1960 JOHNSON 1969) The first attempt to [illegible] an arteriovenous malformation by stereotactic radiation surgery was performed [illegible] 1970 Following radiation surgery directed towards two feeding arteries with a ga[illegible] dose of 45 Gy (4 500 rad) angiography after 18 months demonstrated that the m[illegible] formation had been completely obliterated Both this case and one of arterial an[illegible] treated with the same technique have been reported previously (STEINER et coll 19[illegible]

While more clinical experience has now been gained the optimum radiation d[illegible] for prompt obliteration of the pathologic vessels remains to be determined A se[illegible] of animal experiments has therefore been designed to establish the appropria[illegible] d[illegible] level

Methods

Irradiation Halothane intubation anesthesia was instituted after a short expos[illegible] of the cats to ether Head fixation was provided by a modified stereotactic instrum[illegible]

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Fig 1 The relative dose diagram superimposed upon the stereotactic skull film of the cat The target point is placed close to the midpoint of the clivus and the basilar artery is situated within the 90 per cent isodose curve The concentric rings indicate the 10 50 and 90 per cent relative isodose curves respectively

fork construction in the mouth applying pressure between the palate and the arcus zygomaticus In the radiologic localization of the basilar artery the posterior part of the sella turcica and the clivus were used as reference points on the vertical axis (Fig 1) and the midpoint on the horizontal axis The target point was placed 4 mm below the sella and between one and two mm above the surface of the clivus

The animals were positioned in the gamma unit (Leksell 1971) in the same manner as patients irradiated and immediately afterwards awakened The dose varied from 100 to 300 Gy and the time of survival from 7 to 200 days Thirteen cats were irradiated while two served as untreated controls If both basilar and carotid arteries were occluded the animal became decerebrate with a prominent degree of rigidity The animals were killed by an intraperitoneal overdose of barbituric acid (mebumal)

Histology Burr holes were placed in two or three sites over the convexity and the skulls were kept in formalin 10 % for at least one week The brains were then removed and the pons sectioned into 3 or 4 parts for microscopy

The tissue specimens were fixed in neutral 10 per cent formalin embedded in paraplast sectioned at 4 μm and stained with hematoxylin-eosin and according to the van Gieson method In most cases special staining with Masson s trichrome MSB Goldner s trichrome Mallory s azan and PAS techniques were also used

Formalin fixed tissues which as judged from the light microscopy were of particular interest were cut out from the paraplast and reprocessed for electron microscopy after a method described by the REP institutes of the Organization for Health Research TNO in the Netherlands Pieces of 1 to 3 mm^3 were cut out and deparaffinized in xylene for 24 h rehydrated in a graded series of ethanol in concentrations from 99 per cent to 30 Refixation was carried out in glutaraldehyde 2 in 0 1 M cacodylate buffer for 1 to 2 h followed by osmiumtetroxide 1 % in 0 2 M cacodylate for 1 h The small blocks were dehydrated in a graded series of ethanol in

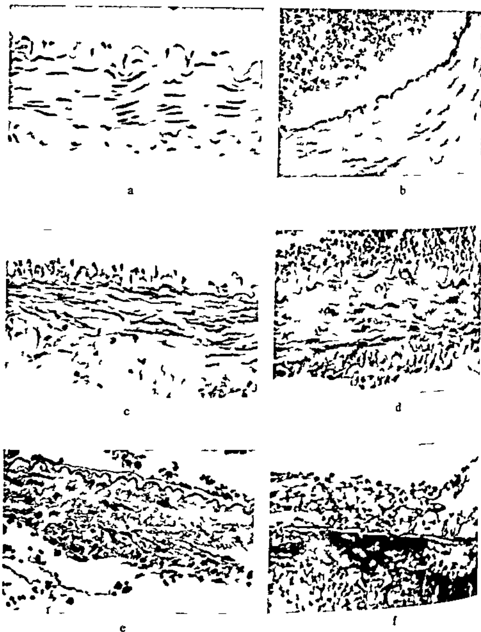


Fig. 2. a) Basilar artery of normal cat control Van Gieson ×335 b) Basilar artery 77 da[illegible] 100 Gy Swollen muscle cell nuclei with low affinity for the stain Swollen, pycnotic end [illegible] nuclei Elastic lamina inconspicuous Intima slightly thickened Van Gieson ×335 c) 16 days [illegible] 200 Gy Endothelium severely damaged and partly disintegrating Elastic lamina almost com[illegible] disappeared The nuclei of the media loosely arranged and vacuolized slender and hyperch[illegible] Van Gieson 335 d) 7 days after 300 Gy Endothelial lining moderately injured with chang[illegible] nuclear polarity Media vacuolized and many nuclei excentrically situated Van Gieson [illegible] e) 89 days after 250 Gy Almost complete necrosis of the vascular wall Hematoxylin-eosin f) 81 days after 200 Gy Media and endothelial lining completely necrotic and the elastic la[illegible] almost invisible Intima replaced by numerous thread like structures and cells with a pale sta[illegible] cytoplasm. Goldner s trichrome ×335

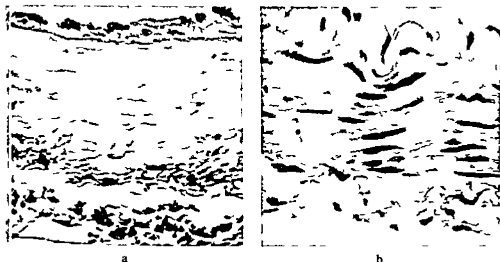


Fig. 3 a) Basilar artery 27 days after 100 Gy Media swollen and edematous with low stainability Edematous adventitia Endothelium pycnotic intima swollen with a few (possibly migrating) cells Tunica elastica poorly defined Van Gieson 870 b) Normal basilar artery for comparison Van Gieson ×870

concentrations from 30 to 99 per cent and embedded in Spurr plastic medium Sections at an approximate thickness of 600 Å were cut stained in alcoholic solution of uranyl acetate by lead citrate according to VENABLE & COGGESHALL (1965) and photographed in a Philips E M 201 at low magnifications (3 000 ×–7 000 ×)

Results

Dose 100 Gy—1 cat The animal was killed 27 days after irradiation The endothelium of the basilar artery in the most severely irradiated area was swollen with very small hyperchromatic pycnotic or disintegrating nuclei and an almost invisible elastic lamina (Fig 2 b) In the intima relatively large pale staining cells with leptochromatic nuclei were sometimes discernible (Fig 3 a) The nuclei of the muscle cells of the media were swollen and as compared with the normal material in general had a low affinity for the stain (Figs 2 b 3 a) In some cases fibrosis was observed in the adventitia and peri and paraadventitial tissues In the brain tissue just above the basilar artery a marked adventitial fibrosis was found in a group of medium sized to small vessels No vascular occlusions were found The brain tissue seemed to be morphologically intact

Dose 200 Gy—8 cats Four cats were killed 14 to 20 days after the irradiation In three of these cats the endothelium of the basilar artery was damaged with many pycnotic nuclei and disintegrating cells the orientation of which was also changed to a more or less upright position with their long axis pointing into the lumen

of the vessel (Fig 2 c) The internal elastic lamina was swollen and partially split The media was edematous and the muscle cells were strongly vacuolized with pencil shaped and on account of the vacuoles often excentrically situated nuclei (Fig In one of the cats fine red medial deposits were discernible with Goldner and staining and with MSB stainings a fibrin positive hyaline material was observed (Fig 5)

An area of necrosis was situated bilaterally just above the basilar artery in which practically all vascular structures were destroyed Along the border with normal tissues most vessels were heavily damaged and many of them partly or completely occluded by thickening of the intima The muscular coat of the vessels was strongly vacuolized In the border zone many vessels were surrounded by perivascular cuffs containing mononuclear cells including trypan blue engulfing macrophages a few plasma cells (Fig 7)

Three cats were investigated 93 to 96 days after irradiation Generally the endothelial tissue was severely damaged In spite of this no definite thrombosis found However in the lumen of the basilar artery in one cat red cells, granulocytes and obvious fibrin were accumulated but thrombocytes were not found. In another cat a plasma plug was found containing aggregated thrombocytes but no fibrin these cats a fibrotic induration of varying degree was found in the basilar artery mainly in the adventitia In one cat the media was strongly vacuolized with a loss of muscular cell nuclei and small irregular areas of hyalinization

In all cats a semicircular area of necrosis was found in the brain tissue distributed above the basilar artery Along the border between intact and necrotic tissue a strong glial reaction with numerous foam cells was present Characteristically the vessels within the brain parenchyma were more severely damaged than larger vessels such as the basilar artery Usually vascular fibrosis of varying degree was observed in many of the vessels In one cat with severe fibrosis, numerous vascular lumina were also more or less occluded Fairly large vascular cuffs, mainly consisting of mononuclear cells and plasma cells were also discernible In another cat conspicuous large areas of edema rich in protein were found particularly in the Virchow Robin spaces the vascular walls also were heavily permeated

One cat was killed 220 days after irradiation In the subarachnoid space hemorrhages and hyperemia existed At certain spots within these bleedings there were aggregations of thrombocytes and precipitation of fibrin. The source of the bleeding could not be detected The basilar artery and its nearest surroundings were fibrotic The media was necrotic had a homogeneous structure and was markedly hyalinized A few endothelial cells coated the intima, which was much widened and contained a large number of elongated swollen granulated cells the majority of which were in various stages of disintegration A few cells nearest to the lumen seemed morphologically intact Toluidine stained sections for electron microscopy revealed that these cells might be smooth muscle cells in a network of thread like (elastic?) structures (Fig 4) Intermingled in this network of cells were a few actively phagocytic



Fig. 4

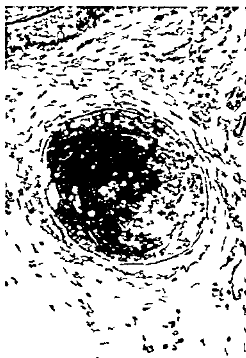


Fig 5

Fig 4 Basilar artery 2_0 days after 200 Gy Media hyalinized and necrotic Tunica elastica partly disrupted Intima strongly thickened by numerous slightly elongated cells (smooth muscle cells) and thread like structures (possibly musculo-elastic thickening) 2 / m Ultratome section Toluidine blue ×900

Fig. 5 Branch of basilar artery 220 days after 200 Gy Arterial hyalinosis and intimal cushion consistin mainly of structureless material 2 / m Ultratome section Toluidine blue 900

monocytes and granulocytes The elastic lamina was mottled at numerous places and at a few sites disrupted No thrombosis was detected A few smaller vessels in the region surrounding the basilar artery were also heavily damaged hyalinized, and more or less completely occluded (Fig 5) In the meninges and the necrotic brain tissue above the basilar artery infiltration and vascular cuffings with mononuclear cells were found

Dose 250 Gy—1 cat One cat was irradiated with 250 Gy and killed on day 89 after the irradiation In this animal the basilar artery was severely damaged with complete destruction of the endothelium and necrosis of the media (Fig 2 c) The adventitial tissue was strongly fibrotic as well as the neighbouring parts of the meninges In the brain tissue above the vessel a necrotic area containing an edema rich in protein was found

Dose 300 Gy—2 cats The cats were killed 7 and 20 days after irradiation respectively In the cat killed on day 7 two different series of sections were examined In one of these no lesions were detected but in the other the endothelium was moderately



Fig 6

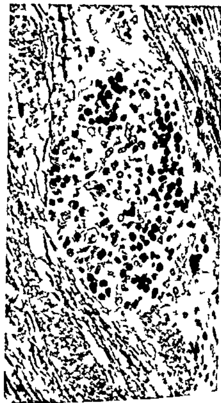


Fig 7

Fig 6 Intrapontine arterioli 20 days after 300 Gy Arterial hyalinosis and edema of the Virchow Robin spaces Azan 565

Fig 7 Intrapontine vessel 81 days after 200 Gy Perivascular cuffing of mononuclear cells and plasma cells Goldner s trichrome 360

damaged with hyperchromatic nuclei with an altered nuclear polarity The endothelium was surrounded by a seam of erythrocytes sticking to the vascular wall The lumen was almost completely filled with red blood cells but no thrombos was found The muscular coat was strongly vacuolized (Fig 2 d) A large area of necrosis with multiple perivascular hemorrhages was situated deep in the brain tissue

In the other cat killed on day 20 a large necrotic area with conspicuous hemorrhages and edema debris and numerous foam cells was located bilaterally above the basilar artery The walls of the smaller arteries of the brain parenchyma were strongly hyalinized and the elastic lamina was split up and disintegrated in certain parts (Fig 6) The lumen of numerous smaller vessels was partially or completely occluded by a fibrin positive material and in many instances surrounded by perivascular cuffing of mainly mononuclear cells (Fig 7) The endothelium of the basilar artery was moderately damaged and the media contained numerous hyperchromatic and a few pycnotic muscle cell nuclei Slight vacuolization and hyalinization of the media was also obvious



Fig 8 14 days after 200 Gy Splitting up of tunica elastica interna (→) with interposition of a smooth muscle like cell containing tonofilaments and vesicles along the cytoplasmic membrane Two endothelial cells Electron micrography of previously paraplast-embedded material 9 000

Discussion

Most of the vessels which were the target of the gamma irradiation showed moderate to severe lesions of essentially the same type as has been described previously (GASSMANN 1899 THIBAUDEAU & MATTICK 1929 TULLIS 1949 THOMAS & FORBUS 1959 ROSEN et coll 1964 MOSTOFI 1966) The lesions seem to involve cell layers of the vascular wall and include endothelial swelling vacuolization degeneration and desquamation rupture and splitting up of the elastic lamina as well as abnormalities in the muscular coat such as vacuolization hyalinization and necrosis However contrary to observations made by ROSEN et coll and MOSTOFI thrombosis formation was not found in this series but in agreement with STEWART et coll (1968) a thickening of the intima was observed in a few cases as an obvious expression of late vascular repair It was also notable that the small arteries in the brain parenchyma were more sensitive to radiation than larger vessels such as the basilar artery (BERDJIS 1971) The small vessels were also highly prone to hyalinization and were frequently surrounded by large protein rich fibrin positive effusions

The reason for the frequent observations of vascular hyaline material seems to

depend largely on the high radiation doses administered At these dose levels it is more than probable that the collagen tissue may become largely *denatured* at the same time as the serum proteins and blood lipoproteins *may penetrate through the* lesions deep into the vascular structures thereby *creating favourable conditions for* hyalinization

The meagre signs of regeneration and cellular proliferation in the irradiated vessels also seem to indicate that the irradiation dose had reached an almost sterilizing effect Only in two cats one killed on day 81 and one on day 220 after irradiation were there obvious signs of vascular repair consisting of a thickening of the intima probably produced by a musculo elastic proliferation preceded by damage or disruption of the elastic lamina Repair or regeneration of this type is often observed in vascular structures following vascular transplantation (JENNINGS & FLOREY 1971) and in the coronary arteries of aging dogs (JÖNSSON 1972) GILLMAN et coll (1955) also observed fragmentation of the elastic lamina and a formation of new (*reduplicated*) *fibers with increasing* age in humans In addition to these changes of the *internal elastic* membrane in dogs JÖNSSON also described smooth muscle cells from the tunica media proliferating through the fragmented elastic membrane forming thickening of the intima together with newly formed elastic fibers often in considerable amounts The intimal proliferations in the present series appear to be similar to those described by JÖNSSON with swelling and fragmentation of the elastic membrane of the intima and penetration of smooth muscle cells into the subendothelial (Fig 8) Such a fragmentation and penetration of cells (possibly muscle cells) into the spaces of the damaged elastic membrane were discernible at electron microscopy already 20 days after irradiation

In the cat killed after 220 days there was also evidence of degeneration of the newly formed intimal tissue mainly in the deepest layers which might be related to a gradual impairment of the cellular nutrition with increasing distance from the vascular lumen According to FRENCH (1970) capillary blood vessels are absent at least in the ... of the musculo elastic thickening of the intima and a tendency for the new tissue to degenerate is evident

In spite of the fact that many of the factors which are considered to promote thrombosis seem to have been at hand in these experiments vascular thrombosis was not found This is difficult to explain The crucial point seems to be related to the almost complete absence of thrombocyte adhesions or aggregations Mechanisms of importance for the initiation of this system such as the liberation of ADP formation of pro-collagen by endothelial cells and the electrical potentials of the endothelium which are all believed to take part in different steps of thrombocyte aggregation may have been seriously disturbed by the irradiation In future investigations the dependency of these factors will be evaluated

SUMMARY

Irradiation of the basilar artery of cats by stereotactic technique was performed with doses arying from 100 to 300 Gy in a gamma unit Histologically vascular lesions such as vacuoli ation degeneration and desquamation of the endothelium and hyalinization and necrosis f the muscular coat predominated whereas reparatory reactions were relatively sparse hrombosis was completely absent

ZUSAMMENFASSUNG

Die Arteria basilaris von Katzen wurde mit einer stereotaktischen Technik mit Dosen wischen 100 und 300 Gy in einer Gamma Strahlenquelle bestrahlt Histologisch waren askulare Schaden wie Vakuolarisation Degeneration und Desquamation des Endothels nd Hyalinisierung und Nekrosen der Muskelschicht vorherrschend Erholungsreaktionen aren jedoch relativ unbedeutend Eine Thrombose fehlte vollstandig

RESUME

L artère basilaire de chats a été irradiee par une technique stéréotactique à des do es allant e 100 à 300 Gy au moyen d un appareil a rayonnements gamma Histologiquement ce sont es lésions vasculaires telles que la vacuolisation la degenérescence et la desquamation de endothélium et la hyalinisation et la necrose de la tunique musculaire qui ont predominé lors que les reactions de reparation ont été relativement minimes La thrombose a été omplètement absente

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CELL POPULATION KINETICS AND DOSE-TIME RELATIONSHIPS FOR POST-IRRADIATION INJURY OF THE BRACHIAL PLEXUS IN MAN

L COHEN and H SVENSSON

The data on radiation induced lesions of the brachial plexus collected by SVENSSON et coll (1975) supplemented by the reports of STOLL & ANDREWS (1966) and MCDERMOTT (1971) together provide sufficient statistical material to derive realistic estimates for the associated cell lethality and repopulation parameters in the irradiated tissues For this type of analysis it is necessary to assume that when a number of different fractionation schemes all yield a similar end result or a standard reaction the cellular surviving fractions at the end of treatment are about the same in each instance The computed cellular surviving fraction can then be correlated with observed response rates using algebraic or statistical methods to fit appropriate parameters in the survival kinetic equations A detailed description of this method was given by COHEN & REDPATH (1977) the basic definitions and relations are described in the following

In the composite multi target model formula for cellular radiation lethality the surviving fraction (S_1) after a single exposure of D_1 Gy is given by the equation

$$S = e^{-JD_1} \times [1 - (1 - e^{-KD})^N] \tag{1}$$

where J (Gy^{-1}) is a measure of the initial slope of the survival curve associated with the irreparable component of cellular radiation injury K (Gy^{-1}) the slope for the sublethal component and N the extrapolation number With fractionated treatment, say W exposures at intervals averaging V days the cellular surviving fraction al

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lowing for repopulation in the intervals between treatments is given by the recurs logistic function

$$S_W = \prod_{i=1}^{W-1} \left[\frac{S_i H_i}{S_i + (H_i - S_i)e^{-YL}} \right] \qquad ($$

The asymptotic limit to repopulation in each interval is defined by H_i where H_i ... and not greater than $e^G \times \prod_{j=1}^{i}(S_j)$ L is the regeneration rate constant (day⁻¹) and G the limiting number of cell cycles available for repopulation

These equations are readily solved numerically and computer programs have be[en] devised to calculate cellular surviving fractions to determine biologically equivale[nt] treatment schemes, to derive cell population kinetic parameters from reactions ob[-] served under various experimental conditions and to determine best fitting values for these parameters from available clinical statistics The RAD3 parameter search program (COHEN, in preparation) provides best fitting estimates for the surviv[ing] fraction of the hypothetical cell population at risk and the associated mean cellul[ar] lethal dose [$D_0 = 1/(J+K)$] slope ratio [initial terminal slope $= J/(J+K)$] extra- polation number (N) regeneration rate constant (L) and repopulation limit (G)

The search program occasionally reveals more than one combination of parameters which fit the data equally well The implicit assumption that the model with para- meters derived from clinical data simulates actual cell lethality and repopulation processes may not always be valid It is possible therefore that the model merely represents a parametrized version of an empirical iso-effect function *fitted to the* observations The system could of course be tested and the relevant parameters confirmed by more direct experimental methods In any event iso-effect t... generated by using the model with parameters derived specifically for the tissue *analysed should be adequate and provide realistic estimates for tolerance lim...d* the tissues concerned

Materials and Methods

Available data comprised a total of 311 annotated cases in whom the response t[o] various doses of radiation delivered to the brachial plexus through supraclavic[ular] and axillary portals using a variety of fractionation schemes and treatment time[s] was recorded The data set could be divided into 16 groups each associated with a particular dose and fractionation scheme These were then *tabulated noting* ... each group the dosage received by the brachial plexus the number of fractions th[e] t... treatment time the gap if any between split courses and the *proportion of pat[ients]* so treated exhibiting a significant neurologic defect

The material was analyzed by means of the RAD3 search program wh... best fitting values of the parameters in eqs (1) and (2) while *searching sequentia[lly]* through a wide range of combinations of parameters This *program com...* tentative surviving fraction (considered a dose level for probit analysis) f... ea[ch]

Table

Printout of iso-effect table comprising tolerance doses (Gy) and total treatment times in days (d) for 8 standard fractionation schedules and various fraction numbers (F No) The third column represents a conventional iso-effect curve for daily treatment (5 times a week) and provides data for the Figure

F	Cont		2/day		Daily		3/week		2/week		Weekly		Int = 2 weeks		Monthly	
No	Gy	d	Gy	d	Gy	d	Gy	d	Gy	d	Gy	d	Gy	d	Gy	d
3	36 5	1 4	36 5	2	37 5	4	38	6	39	8	42	15	48	29	59 5	57
5	41	1 8	41 5	3	42.5	6	44 5	10	46 5	15	52 5	29	64 5	57	80 5	113
8	46	2 4	47	4 5	49.5	10	52 5	17	56 5	26	67 5	50	86 5	99	88	197
12	51	3 2	52 5	6.5	57	15	62.5	26	69	40	87	78	96	155	96	309
17	55.5	4 2	58	9	65 5	22	74	38	83 5	57	104	113	104 5	225	104 5	449
23	59.5	5 4	63 5	12	74	30	86 5	52	101	78	112	155	112	309	112	617
30	63.5	6 8	69	15 5	84	39	101	68	117	103	119	204	119	407	119	813
38	67	8 4	74 5	19.5	94 5	49	117	86	125 5	131	125 5	260	125 5	519	125 5	1 037
47	70	10 2	80 5	24	106	61	130	107	131 5	162	131 5	323	131 5	645	131.5	1 289
57	73	12 2	86	29	118 5	74	136	130	136	197	136	393	136	785	136	1 569
68	76	14 4	92	34 5	131	88	140 5	155	140 5	236	140 5	470	140 5	939	140 5	1 877
80	79	16 8	98 5	40 5	141 5	104	144	183	144	278	144	554	144	1 107	144	2 213
93	82	19 4	105	47	146 5	121	147	213	147	323	147	645	147	1 289	147	2 577

treatment scheme and then fits the observed proportion of reactors to these using a multi probit procedure Best fitting parameters in this context are those which yield the steepest dose response relationship and smallest chi square estimate in the analysis

The parameters derived by the preceding operation were then used in the iso-effect program (RAD1) to compute a table of equivalent doses or brachial plexus tolerance limits for a range of fractionation schemes This program also finds an approximate linear fit of the tabulated results to the empirical power function (ELLIS NSD equation 1968) and calculates suitable values for the nominal standard dose and exponents

Results

Results of the search program for radiation injury of the brachial plexus suggest that best fitting parameters for this series are $D_0 = 2\ 73$ Gy extrapolation number $N = 3$ regeneration rate constant $L = 0\ 15$ day^{-1} parameter ratio $K/J = 1\ 46$ and repopulation limit $G = 14$ cell cycles From these figures the slope ratio $J/(J+K) = 0\ 41$ the initial slope of the lethality curve $J = 0\ 15$ Gy^{-1} and the terminal slope $J+K = 0\ 37$ Gy^{-1} are derived The computed median value (50 per cent significant injury) for the log surviving fraction ($Q = -\log_{10} S$) of the hypothetical cell population affected is then 4 43 with a standard deviation of 2 13

The iso-effect table generated by using the foregoing parameters in the RAD1

lowing for repopulation in the intervals between treatments is given by the recursive logistic function

$$S_W = \prod_{i=1}^{W-1} \left[\frac{S_i H_i}{S_i + (H_i - S_i) e^{-tL}} \right] \quad (2)$$

The asymptotic limit to repopulation in each interval is defined by H_i where $H_i \geq 1$ and not greater than $e^G \times \prod_{i=1}^{i-1}(S_i)$. L is the regeneration rate constant (day^{-1}) and G the limiting number of cell cycles available for repopulation.

These equations are readily solved numerically and computer programs have been devised to calculate cellular surviving fractions to determine biologically equivalent treatment schemes to derive cell population kinetic parameters from reactions observed under various experimental conditions and to determine best fitting values for these parameters from available clinical statistics. The RAD3 parameter search program (COHEN in preparation) provides best fitting estimates for the surviving fraction of the hypothetical cell population at risk and the associated mean cellular lethal dose [$D_0 = 1/(J+K)$] slope ratio [initial terminal slope $= J/(J+K)$] extrapolation number (N) regeneration rate constant (L) and repopulation limit (G).

The search program occasionally reveals more than one combination of parameters which fit the data equally well. The implicit assumption that the model with parameters derived from clinical data simulates actual cell lethality and repopulation processes may not always be valid. It is possible therefore that the model merely represents a parametrized version of an empirical iso effect function fitted to the observations. The system could of course be tested and the relevant parameters confirmed by more direct experimental methods. In any event iso-effect tables generated by using the model with parameters derived specifically for the system analysed should be adequate and provide realistic estimates for tolerance limits of the tissues concerned.

Materials and Methods

Available data comprised a total of 311 annotated cases in whom the response to various doses of radiation delivered to the brachial plexus through supraclavicular and axillary portals using a variety of fractionation schemes and treatment times was recorded. The data set could be divided into 16 groups each associated with a particular dose and fractionation scheme. These were then tabulated noting in each group the dosage received by the brachial plexus the number of fractions the total treatment time the gap if any between split courses and the proportion of patients so treated exhibiting a significant neurologic defect.

The material was analyzed by means of the RAD3 search program which finds best fitting values of the parameters in eqs (1) and (2) while searching sequentially through a wide range of combinations of parameters. This program computes a tentative surviving fraction (considered a dose level for probit analysis) for each

meters derived from fairly routine clinical follow up data The iso-effect Table can then be used as a set of tolerance dosage limits for late effects in irradiated peripheral nerve

Acknowledgement

The authors are grateful to Professor L.-G Larsson and Dr P Westling for their careful follow up of the cases, which made this report possible

SUMMARY

Collected data on radiation induced lesions of the brachial plexus were analyzed on the assumption that this reaction arises from depletion of some unidentified cell population in the irradiated tissues A multi probit search program was used to derive best fitting cell kinetic parameters in a composite multi target model for cellular radiation lethality and repopulation. From these parameters a comprehensive iso-effect table for a wide range of treatment schedules including daily treatment as well as fractionation at shorter and longer intervals was constructed The table provides a useful set of tolerance dosage limits for late effects in irradiated peripheral nerve

ZUSAMMENFASSUNG

Die gesammelten Daten der strahlinduzierten Veranderungen des Plexus brachialis wurden unter der Annahme dass diese Reaktion durch die Entfernung einer nicht identifizierten Zellpopulation im bestrahlten Gewebe hervorgerufen wird analysiert. Ein Mutli Probit Programm wurde verwendet um die besste Anpassung an zellkinetische Parameter in einem zusammengesetzten Multi Target Model fur die zellulare Strahlenletalitat und Repopulation festzustellen Aus diesen Parametern wurde eine zusammenfassende Iso-Effekt Tabelle konstruiert, die einen weiten Bereich von Behandlungschemata einschliesslich taglicher Behandlung sowie Fraktionierung mit kürzeren und längeren Intervallen umfasst Diese Tabelle bietet eine nutzliche Zusammenstellung der Toleransdosengrenzen für Spat effekte in bestrahlten peripheren Nerven

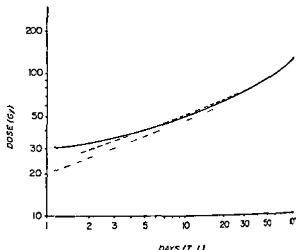
RESUME

Les donnees recueillies sur les radio-lesions du plexus brachial ont ete analysees dans l'hypothese que cette reaction est due a la depletion d une population cellulaire non identifiee dans les tissus irradies Un programme de recherches multi probits a ete utilise pour deduire les parametres de la cinetique cellulaire qui conviennent le mieux dans un modele composite multi-cibles pour la lethalite cellulaire par les radiations et pour la repopulation. A partir de ces parametres les auteurs ont construit un vaste tableau iso-effet pour une large gamme de schemas de traitements comprenant un traitement quotidien aussi bien qu un fractionnement a des intervalles plus courts ou plus longs Le tableau donne une serie utile de limites de tolerance de doses pour les effets retardes des nerves peripheriques irradiees

REFERENCES

COHEN L. Derivation of cell population kinetic parameters from clinical statistical data (Program RAD3) To be published in Int J radiat Oncol (1978)

— REDPATH J L. Derivation of survival kinetic parameters for cell populations by computer simulation of radiobiological data. Radiat. Res 69 (1977) 387



Computed iso-effect curve for 50 per cent risk of radiation injury to the brachial plexus treated 5 times a week (—) The equivalent single dose (EQ DI) is 30 Gy the best linear approximation (STRANDQVIST) to the iso-effect function is given by a nominal single dose of 23 Gy and slope of 0 37 ( ) The CRE value calculated by SVENSSON et coll (21 Gy) and the associated iso-effect line ( ) are shown for comparison

program is shown in the Table This program tabulates computed equivalent doses for a wide range of treatment schemes from 1 to 100 fractions given at various intervals from twice daily to once a month and including continuous irradiation Results for daily treatment are also plotted in the Figure in the form of iso-effect curves relating total dose to over all treatment time The solid line in the Figure then represents the iso effect curve for radiation tolerance of peripheral nerve given daily treatment (5 per week)

Although the iso effect function is curved and not readily fitted by any straight line the nearest match to the ELLIS formula gives an estimated NSD of 23 Gy with *exponents $n = 0\ 25$ and $t = 0\ 12$ These exponents are similar* to those proposed by ELLIS for tolerance of normal tissues An approximate Strandqvist type iso-effect line (STRANDQVIST 1944) can also be derived (Figure) The true equivalent single dose is the origin of the iso effect curve at 30 Gy (well above the NSD value) These single dose equivalents are comparable with the median CRE value (21 Gy) calculated by SVENSSON et coll (1976)

Discussion

The clinical observations upon which this analysis is based appear to be compatible with the hypothesis that radiation injury of the brachial plexus arises from depletion of some as yet unidentified cell population in the irradiated neural or perineural tissues *Possible candidates are connective* tissue fibroblasts endothelial cells of the vascular supply or the supporting neurilemma The cellular surviving fraction computed on this basis is 10^{-6} which is of a similar order to that associated with other severe local reactions (EMERY et coll 1970) The cellular lethality and repopulation parameters fitted to the observations appear to be realistic and not dissimilar to those derived for other mammalian tissues (COHEN & REDPATH 1977)

The particular value of the foregoing analysis is its potential for generating non-linear iso-effect functions for a wide range of fractionation schemes using par-

REPORT TO THE INTERNATIONAL EXECUTIVE COMMITTEE OF THE FOURTEENTH INTERNATIONAL CONGRESS OF RADIOLOGY FROM THE INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS

The period since the XIIIth International Congress of Radiology has been a very active one for the International Commission on Radiation Units and Measurements (ICRU) The Commission s program has moved forward significantly since the last Congress and this report represents an effort to summarize the Commission s activities since 1973

Published reports

Since 1973 the ICRU has published three scientific and technical reports

ICRU Report 24 Determination of Absorbed Dose in a Patient Irradiated by Beams of X or Gamma Rays in *Radiotherapy Procedures*
ICRU Report 25 Conceptual Basis for the Determination of Dose Equivalent
ICRU Report 26 Neutron Dosimetry for Biology and Medicine

ICRU Report 24 is the second of a series of reports intended to cover the steps pertaining to dosimetry in the radiation therapy clinic from the determination of the output of the therapy machine to the assessment of the absorbed dose in the patient The first report of the series ICRU Report 23 (Measurement of absorbed dose in a phantom irradiated by a single beam of roentgen or gamma rays) treats procedures relating to the determination of the absorbed dose at any point in a cuboid water phantom ICRU Report 24 is concerned with the transition from the water phantom to the human patient A third report now in preparation will discuss the criteria which determine the target volume and the specifica tion of the dose within that volume ICRU Report 24 includes major sections on the basic data derived from water phantom measurements patient data combination of basic data and patient data combinations of single beams planning and delivery of radiation therapy and errors in clinical dosimetry The report also contains an extensive glossary defining terms used in the report

ICRU Report 25 is concerned with the physical quantities employed in radiation protec tion their applicability to various irradiation conditions and their inter relationships The

report seeks to clarify the terminology used in radiation protection practice and to minim... the ambiguities often introduced as a result of the use of simplifying assumptions The report contains major sections on the dose equivalent quantities and their inter relationships the index quantities and their utilization and the determination of dose equivalent index ICRU Report 25 also includes appendices treating the hierarchy of radiation quantities the specification of absorbed dose and the effect of angular distribution of the incident radiation

ICRU Report 26 treats the currently available methods for determining absorbed dose and kerma of fast neutrons employed for radiobiological and medical applications The objective of neutron absorbed dose determinations is to describe the energy deposition in irradiated material in such detail that workers in biology and medicine may make unambiguous correlations with observed responses or predictions of responses of irradiated biological systems This implies that the selection of methods employed for this dosimetry and the numerical data to be registered will depend to a large extent on the object irradiated and on the end point observed ICRU Report 26 gives guidance in connection with the selection of an appropriate dosimetric method The report covers the field of neutron dosimetry in biology and medicine in a comprehensive way Basic concepts and definitions employed in neutron dosimetry are summarized as are the principles of the experimental technique employed The report also includes descriptions of the methods and instrumentation and characteristics of instruments with reference to random and systematic uncertainties energy dependence and sensitivity to gamma radiation Appropriate techniques for monitoring the radiation conditions during dosimetry measurements or irradiations of biological objects are described in the report The resport also treats specific features of different neutron sources and specific problems of neutron dosimetry in radiation biology and radiation therapy

Some assessment of the acceptance of published ICRU Reports by the scientific community is given by the sales records for ICRU Reports A report on the number of copies distributed is set out in the Annex

In process of publication Three other reports are expected to become available soon in published form The first of these projects is the international neutron dosimetry intercomparison Interest in using neutrons for biology and medicine has been increasing in the last few years However generally accepted standards for neutron dosimetry did not exist As a result the ICRU determined to sponsor and international neutron dosimetry intercomparison which was intended to compare the results obtained by various individuals or groups in performing absolute fast neutron dosimetry The intercomparison was carried out in 1973 with fourteen groups of scientists participating Subsequently the results were analyzed and a report prepared Work on that report is now completed and the result is to be published as ICRU Report 27 (An international neutron dosimetry intercomparison) The Report is now in press and is expected to become available soon

The second of the recently completed efforts involved the development of ICRU recommendations on high energy radiation dosimetry This work resulted in the development of ICRU Report 28 (Basic aspects of high energy particle interactions and radiation dosimetry) This report deals with the fundamental considerations underlying the dosimetry of radiations having energies in excess of about 10 eV A substantial portion of the report deals with the physics of high energy radiation with particular emphasis on [illegible] aspects However the report also treats the radiation environment surrounding accelerators in space and at supersonic aircraft altitudes Finally the report presents an analysis of the problem of dose equivalent specification and a survey of absorbed dose and dose equivalent measurement techniques The report carries two appendices stopping powers for

Annex

Distribution of ICRU reports during the period January 1 1977 through August 31 1977

CRU Report No	Title and Year of Publication	Number of Copies Distributed			
		U.S Government Printing Office[a]	ICRU Publications Office[b]		Both Sources Combined Total
			September 1 1976 through August 31 1977	Total[c]	
1	Discussion of International Units and Standards for X ray Work (1927)	—[e]	—[d]	—	—[e]
2	International X ray Unit of Intensity (1928)	—	—[d]	—	—
3	Report of Committee on Standardization of X Ray Measurements (1934)	—	—[d]	—	—
4	Recommendations of the International Committee for Radiological Units (1934)	—[e]	—[d]	—	—[e]
5	Recommendations of the International Committee for Radiological Units (1937)	—	—[d]	—	—[e]
6	Recommendations of the International Commission on Radiological Units (1951)	4 255	—[d]	—[f]	4 255
7	Recommendations of the International Commission on Radiological Units (1954)	—	—[d]	—	—[e]
8	Report of International Commission on Radiological Units and Measurements (1956)	11 740	—[d]	—[f]	11 740
9	Report of the International Commission on Radiological Units and Measurements (1961)	6 700	—[d]	—[f]	6 700
0a	Radiation Quantities and Units (1962)	14 884	—[d]	—[f]	14 884
0b	Physical Aspects of Irradiation (1964)	14 86[illegible]	223	1 915	16 777
0c	Radioactivity (1963)	16 189	167	1 642	17 831
0d	Clinical Dosimetry (1963)	19 714	232	1 809	21 523
0e	Radiobiological Dosimetry (1963)	20 900	184	1 391	22 291
0f	Methods of Evaluating Radiological Equipment and Materials (1963)	8 418	384	2 534	10 952
1	Radiation Quantities and Units (1968)	—[g]	—[d]	6 052	6 052

Annex (*cont.*)

ICRU Report No	Title and Year of Publication	Number of Copies Distributed			
		U.S. Government Printing Office[a]	ICRU Publications Office[b]		Both Sources Combined Total
			September 1 1976 through August 31 1977	Total[c]	
12	Certification of Standardized Radioactive Sources (1968)	—[g]	188	3 850	3 850
13	Neutron Fluence, Neutron Spectra and Kerma (1969)	—[g]	307	3 648	3 648
14	Radiation Dosimetry: X Rays and Gamma Rays with Maximum Photon Energies Between 0.6 and 50 MeV (1969)	—[g]	349	5 091	5 091
15	Cameras for Image Intensifier Fluorography (1969)	—[g]	181	3 6 0	3 620
16	Linear Energy Transfer (1970)	—[g]	243	3 181	3 181
17	Radiation Dosimetry: X Rays Generated at Potentials of 5 to 150 kV (1970)	—[g]	255	4 0_5	4 0_5
18	Specification of High Activity Gamma Ray Sources (1970)	—[g]	196	2 989	[illegible]
19	Radiation Quantities and Units (1971)	—[g]	462	6 687	[illegible]
20	Radiation Protection Instrumentation and Its Application (1971)	—[g]	244	5 707	[illegible]
21	Radiation Dosimetry: Electrons with Initial Energies Between 1 and 50 MeV (1972)	—[g]	342	2 9 9	[illegible]
22	Measurement of Low Level Radioactivity (1972)	—[g]	2?4	?495	[illegible]
23	Measurement of Absorbed Dose in a Phantom Irradiated by a Single Beam of X or Gamma Rays (1972)	—[g]	432	2 368	[illegible]
19 S	Dose Equivalent (1973)	—[g]	388	2 9 8	[illegible]
24	Determination of Absorbed Dose in a Patient Irradiated by Beams of X or Gamma Rays in Radiotherapy Procedures (1976)	—[g]	2 117	2 117	[illegible]
25	Conceptual Basis for the Determination of Dose Equivalent (1976)	—[g]	1 995	1 995	[illegible]
26	Neutron Dosimetry for Biology and Medicine (1977)	—[g]	968	968	[illegible]
Total		117 662	10 091	69 971	[illegible]

rotons and mass energyabsorption coefficients The printer s manuscript of the report just been completed and thus the report will soon be in press

The third report is concerned with the development of ICRU recommendations on thods of assessment of dose in tracer investigations Assessment of absorbed dose in inical use of radionuclides The report is concerned with the methods of evaluating the sorbed dose received by the tissues of persons to whom radiopharmaceuticals are ad inistered The resport includes basic concepts and formulae a critical account of the ethods used in obtaining the biological data needed for calculations of dose summaries f the actual procedures recommended for the calculations and information on the limitations ad difficulties involved in such an assessment It is hoped that the report can be published the near future

Current program

The Commission has divided its field of interest into eleven areas and assigned one or ore members of the Commission to serve as sponsor for each area A body of consultants s been constituted for many of these areas to advise the Commission on the need for RU recommendations relating to the specific area and on the means for meeting an entified need Each area is reviewed periodically by its sponsors and selected consultants ecommendations of such groups for new reports are then reviewed by the Commission d priorities assigned

The areas of interest are

adiation therapy
adiation diagnosis
adioactivity
uclear medicine
adiation biology
adiation physics—roentgen rays gamma rays and electrons
adiation physics—neutrons and heavy particles
adiation protection
alues of factors—W S etc
heoretical aspects
uantities and units

The actual preparation of ICRU Reports is carried out by report committees The rrently active report committees are as follows

verage energy required to produce an ion pair
omputer uses in radiation therapy

The figures given exclude reports purchased by the ICRU Publications Office for subsequent sale except for the period January 1 1969 through December 31 1970 The Government Printing ffice does not maintain monthly distribution breakdowns and hence distribution during the period ptember 1 1975 to August 31 1977 is not available

Includes distribution of complimentary copies

Since the opening of the ICRU Publications Office in September 1968

Out of print before September 1 1976

Published in a journal and no record of the distribution is available

Out of print prior to opening of the ICRU Publications Office in September 1968

Distributed only by the ICRU Publications Office

Dose specification for reporting
Dosimetry for pulsed radiation
Fundamental quantities and units
High energy electron beam dosimetry
Low level in vivo counting in humans
Microdosimetry
Photographic dosimetry in external beam therapy
Radiobiological dosimetry
Scanning of internally deposited radionuclides
Stopping power

Under investigation are potential new activities relating to the following topics

Absolute and relative dosimetry in the megarad range
Radiation damage
Specification of the performance of fluorescent screens
Definitions and terminology for computed tomography
Determination of dose equivalent index.

As has been the case since 1962 the Commission receives reports from the subgroups at the time of their completion rather than at fixed deadlines Meetings of the Commission and of the subgroups are held as needed Since the XIIIth International Congress of Radiology the Commission has met four times and fiscal support for those meetings has come from several sources

Seattle (1974) Battelle Seattle Research Center of the Battelle Memorial Institute
Washington (1975) Pan American Health Organization
Brussels (1976) Commission of the European Communities
Teresopolis (1977) Comissão Nacional de Energia Nuclear (Brasil)

International System of Units

Following an extensive investigation the General Conference of Weights and Meas[illegible] —the diplomatic organ of the Metre Convention—proposed for worldwide use the In[illegible] national System of Units (SI) In this system the units for any quantity can be ex[illegible] terms of the product and quotient of seven base units The special units curie rad, r[illegible] and roentgen are not compatible with the International System of Units and the [illegible] SI are reciprocal second joule per kilogram joule per kilogram and coulomb per kil[illegible] respectively After the action of the General Conference authorities in the various c[illegible] immediately began considering legal adoption of the SI units Recognizing that few me[illegible] of the radiation community were fully cognizant of this proposed trend the ICRU [illegible] comments on the change and endeavored to outline possible alternatives From the c[illegible] ments received it appeared that the majority wished to change to the SI system if sp[illegible] names could be adopted for these four units Therefore the ICRU developed ap[illegible] and suggested names for the SI units used for activity and absorbed dose In 1975 the Ge[illegible] Conference of Weights and Measures approved the use of the name becquerel for r[illegible] second to be used for the specification of activity and of gray as the special name for [illegible] kilogram to be used with ionizing radiation Believing that ionizing radiation is [illegible] a term the ICRU and an advisory committee to the General Conference recommended that the use of gray be limited to absorbed dose absorbed dose index, kerma and [illegible] energy imparted The General Conference has not yet had an opportunity to act on [illegible] recommendation

Following the acceptance of becoquerel and gray the ICRU and ICRP developed the rguments for a special name (sievert) to be used as the unit for dose equivalent These ere forwarded to the General Conference of Weights and Measures through its scientific ommittees There has not yet been time for action to be taken on this proposal

L H Gray medal

The third recipient of the L H Gray medal is Dr Mortimer M Elkind a biophysicist t the Argonne National Laboratory Chicago Illinois USA Dr Elkind received the ward at the XIVth International Congress of Radiology and in response to the Com nission s invitation delivered at the Congress a lecture entitled Molecular and cellular adiobiology of damage repair processes in mammalian cells

ICRU s relationships with other organi ations

In addition to its close relationship with the International Society of Radiology the CRU has developed relationships with other organizations interested in the problems of adiation quantities units and measurement During the period since the XIIIth nternational Congress of Radiology the Commission has continued its collaboration with he International Commission on Radiological Protection on problems of common nterest Since 1955 the ICRU has had an official relationship with the World Health Organization (WHO) whereby the ICRU is looked to for primary guidance in matters of adiation units and measurements and in turn the WHO assists in the world wide dissemi ation of the Comission s recommendations In 1960 the ICRU entered into consultative tatus with the International Atomic Energy Agency The Commission has a formal lationship with the United Nations Scientific Committee on the Effects of Atomic adiation (UNSCEAR) whereby ICRU observers are invited to attend UNSCEAR meet ngs The Commission and the International Organization for Standardization (ISO) in ormally exchange notifications of meetings and the ICRU is formally designated for aison with two of the ISO Technical Committees The ICRU also corresponds and xchanges final reports with the following organizations

Bureau International des Poids et Mesures
ommission of the European Communities
Council for International Organizations of Medical Sciences
Food and Agriculture Organization
nternational Commission on Illumination
nternational Committee of Photobiology
nternational Council of Scientific Unions
nternational Electrotechnical Commission
nternational Labor Office
nternational Radiation Protection Association
nternational Union of Pure and Applied Physics
ional Union of Radiation Sciences
United Nations Educational Scientific and Cultural Organization

The Commission has found its relationship with all of these organizations fruitful and of ubstantial benefit to the ICRU program Relations with these other international bodies lo not affect the basic affiliation of the ICRU to the International Society of Radiology

Commission finances

In the early days of its existence the ICRU operated essentially on a voluntary b with the travel and operating costs being borne by the parent organizations of the p cipants (Only token assistance was originally available from the International Society Radiology) Recognizing the impracticability of continuing this mode of operation on an indefinite basis operating funds were sought from various sources

Financial support has been received from the following organizations

B A T Zigaretten Fabriken GmbH
Commission of the European Communities
Comissao Nacional de Energia Nuclear
Council for International Organizations of Medical Sciences
Eastman Kodak
E I duPont de Nemours
Ford Foundation
General Electric Company
International Atomic Energy Agency
International Radiation Protection Association
International Society of Radiology
Japan Industries Association of Radiation Apparatus
John och Augusta Perssons stiftelse
National Cancer Institute of the U S Department of Health Education and Welfare
N V Philips Gloeilampenfabrieken
Picker Corporation
Radiological Society of North America
Rockefeller Foundation
Siemens Corporation
Society of Nuclear Medicine
Statens lægevidenskabelige Forskningsråd
U S Bureau of Radiological Health of the Food and Drug Administration
World Health Organization

Travel support for ICRU participants has been provided by many organizations, incl the Deutsche Rontgengesellschaft Energy Research and Development Agency (U S National Radiological Protection Board (U K) and the Swedish Cancer Society

In recognition of the fact that its work is made possible by the generous support provided these organizations the Commission expresses its deep appreciation

Recently the ICRU began to realize that the continued inflation throughout the and the stringent budgets available particularly to some governmental organizations had supported ICRU work would require the solicitation of funds from sources previously approached by the Commission It was determined that such a broad solicitation effort would be facilitated if individuals could be identified in various graphical areas who had some knowledge of possible sources and if possible contacts with persons in organizations that might be solicited As a result the Commission determined to establish the ICRU Financial Assistance Group Professor Dr B Combée of the Netherlands accepted the Chairmanship of the Group and sub the following were appointed to membership in the Group Prof John W Bose Kingdom Dr Bryan Will Australia Prof Olle Olsson Sweden Mr Frank D USA and Dr Herma Germany Additional appointments are expected to be

ı the near future to provide adequate coverage of other areas of the world It is expected ıat the Financial Assistance Group will play an important role in the fiscal aspects of the CRU program in the future

Membership

For the years 1973 to 1977 the ICRU membership has been

Allisy France	A Kellerer Germany
S Caswell USA (1975–1977)	K Lidén Sweden
I J Dunster United Kingdom	H H Rossi USA
Edholm Sweden	W K Sinclair USA
R Greening, United Kingdom	A Tsuya Japan (1973–1975)
Harder Germany	A Wambersie Belgium
Harper USA	H O Wyckoff USA

Serving as Commission Officers until the XIVth International Congress of Radiology ere

O Wyckoff Chairman	K Liden Secretary
Allisy Vice Chairman	W R Ney Technical Secretary

During the 1969 meeting of the Commission L S Taylor was elected Member Emeritus ıd Honorary Chairman In 1973 Dr Taylor s appointment as Honorary Chairman was ‹tended to 1977 F P Cowan F Gauwerky R H Morgan and F W Spiers were elected nior Advisors for the period 1973–1977 A Tsuya was elected a Senior Advisor at the me of his resignation from the Commission membership in 1975

Elected to serve during the period between the XIVth and XVth International Con esses of Radiology were the following

New members

Adams United Kingdom
Cowper Canada
van der Schoot the Netherlands

Continuing members

Allisy France	A Kellerer Germany
S Caswell USA	H H Rossi USA
Edholm Sweden	W K Sinclair USA
R Greening United Kingdom	A Wambersie Belgium
Harder Germany	H O Wyckoff USA

Honorary Chairman and Member Emeritus

S Taylor

Senior advisors

J Dunster United Kingdom
Harper USA
Liden Sweden

Commission officers

O Wyckoff Chairman
Allisy Vice Chairman
R Ney Technical Secretary

Outlook for the future

The period since the XIIIth International Congress of Radiology has been one of fruitful progress in the ICRU program The dedication of the individual scientists participating in the Commission s program has been unremitting It constitutes the keystone of the Commission s program The support of the many organizations interested in the work of the ICRU plays an important role in the continuation of the Commission s efforts to develop recommendations on important problems relating to radiation quantities units and measurement techniques

Examination of the scientific aspects of the Commission s program leads to an optimistic evaluation of the outlook for the future The report committee efforts are continuing to *attack in a useful way problems of substantial importance*

Published recommendations of the Commission continue to be recognized as the definitive statement on many important questions Recently undertaken efforts to strengthen the fiscal base of the Commission s operations also lead to an optimistic view of the future If a firm financial base can be established there should be no reason why the Commission cannot continue to discharge its obligations to make widely available recommendations which represent the consensus of leading scientific opinion on questions of radiation quantities units and measurement techniques

Conclusion

In a report of this kind it has not been possible to cover in detail all the activities of the Commission since 1973 However the material presented affords reasonable evidence of the significant progress that has been made by the Commission since the XIIIth International Congress of Radiology *The Commission of course* plans to continue the activities already underway and remain on the alert for other projects in which the ICRU can make significant contributions to scientific progress The maintenance of the current momentum in the ICRU s activities will constitute an important challenge in the future

However the continued support of the many individuals and organizations interested in the Commission s program leads to an optimistic view of the Commission s ability to carry on a useful and fruitful program

October 1977

Respectfully submitted

Harold O Wyckoff
Chairman

A C T A R A D I O L O G I C A

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CARCINOMA OF THE THYROID

A survey of 227 cases

BENTE RASMUSSON

In Denmark thyroid carcinoma accounts for 0 76 per cent of neoplasms in women and 0 3 per cent of neoplasms in men (mean values 1963 to 1967) About 100 new cases occur annually (CLEMMESEN 1969 1974)

Material During the period 1960 to 1970 255 patients with thyroid carcinoma were admitted to this Centre constituting about 30 per cent of all malignant thyroid tumours in Denmark during this period

The material includes all microscopically proven carcinomas of the thyroid in patients with satisfactory preoperative records and controlled at this hospital Six patients with rare types of carcinoma of the thyroid gland were not included (three cases of sarcoma and one case each of squamous-cell Hurthle-cell and embryonal carcinoma) In all 28 patients were excluded

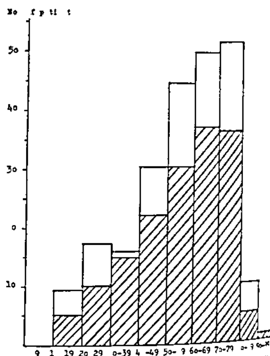
The clinical staging representing a modification of MCWHIRTER's staging (1969) used at this hospital is given in Table 1

Age and sex distribution In the whole material the female/male ratio was 2 [illegible]/1 and the mean age at diagnosis was 56 years (Figure Table 2) This means a somewhat higher mean age than in the reports by WOOLNER et coll (1961, 46 years), [illegible] (1969 52 years) and FRANSSILA (1971 54 years)

Microscopy The microscopic classification used was that of WARREN & MEISSNER (1953 1969) and it was performed at the pathologic departments either at the

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From the Radium Centre Finsen Institute DK 2100 Copenhagen Denmark Submitted for publication 2 August 19 6



Distribution of 227 patients by age and sex ☐ males ▨ females

Finsen Institute or Rigshospitalet The frequency of the different types appears in Table 2

Previous ionizing irradiation Irradiation of the neck is a known etiologic factor in carcinoma of the thyroid gland both in children (SIMPSON & HEMPELMANN 19– WINSHIP & ROSVOLL 1970 REFETOFF et coll 1975) and in adults (BLOCK et al 1969 PARKER et coll 1974)

In the present material 15 patients (6 6 %) had a known history of irradiation of the neck (Table 3) None of the patients had been treated by ^{131}I for hyperthyroidism The indication for previous irradiation was goitre (8 cases) cervical lymphadenitis (5 cases) hypertrophic tonsils (1 case) unknown (1 case) The dose was known in 2 cases only (1 600 R × 2 and 1 800 R × 3 respectively) The number of patients previously irradiated is probably a minimum number since some of the patients may have forgotten an irradiation in their childhood

Gene defects Medullary carcinoma of the thyroid is occasionally associated with other disorders neuromas pheochromocytoma abnormal hormone production and probably bone abnormalities LJUNGBERG et coll (1967) have suggested that medullary thyroid carcinoma in such cases is a genetically determined systemic disease caused by a defect in a single cell system developed from the neural crest and migrating to the foregut where it forms the chromaffin cell system

Table 1

Clinical staging

Stage	Tumour	Cervical lymph nodes	Distant metastases
I	T1	N0	M0
II	T0 T1 or T2	N1 or N2	M0
III	T3	N3	M0
IV			M1

T1 Enlargement of ≤ one half of the gland no extracapsular spread T2 Enlargement of > one half of the gland no extra capsular spread T3 Any enlargement associated with extra capsular spread as indicated by a) limitation of movement of the gland on swallowing b) cord paralysis c) invasion of larynx trachea or esophagus

Table 2

Sex ratio and mean age in the 4 tumour types Percentages given in parentheses

Tumour type	Number	Ratio female/male	Mean age (years)		
			All patients	Women	Men
Papillary	114 (50)	1 9/1	51 1	49 8	53 3
Follicular	43 (19)	3 8/1	59 7	58 4	64 8
Solid	20 (9)	1 2/1	53 4	54 8	51 7
Anaplasti	50 (22)	2.9/1	65 1	66 3	62
Total	227	2 2/1	56	55 9	56 1

In the present material solid carcinoma was diagnosed in 20 patients 11 of these were of the medullary type One or more associated typical disorders were found in 5 of these 11 patients

Pregnancy Eight women 16 per cent of the women under 50 years of age had their first symptom or sign of malignancy in or shortly after pregnancy from 6 months ante partum to 3 months post partum This does not allow any conclusion on pregnancy as an etiologic factor Furthermore the thyroid gland often increases in size during pregnancy This could explain why a previously unobserved tumour becomes visible or palpable

Symptoms The records of 211 patients contained sufficient information (Table 4) Twenty six patients had more than one presenting symptom i e besides growth of a tumour or goitre they had hoarseness dysphagia or symptoms from distant metastases

Table 3

Patients with a known history of irradiation of the neck

Tumour type	No	Per cent	Age (years) at irradiation		Interval (years) from irradiation to diagnosis	
			Mean	Range	Mean	Range
Papillary	8	7	16 3	10–29	21 8	8–30
Follicular	3	7	18 3	10–29	45 3	9–67
Solid	0					
Anaplastic	4	8	31	15–60	36 5	17–45
Total	15	6 6	20 6	10–60	34 5	8–67

Table 4

Initial symptoms in 211 patients Percentages given in parentheses

Tumour type	No	Growth of tumour*	Growth of goitre	Hoarseness	Dysphagia	Symptoms from distant metastasis
Papillary	105	85 (81)	15 (14)	10 (9 5)	4 (3 8)	5 (4 7)
Follicular	39	17 (43 6)	12 (30 8)	1 (2 6)	1 (2 6)	8 (20 5)
Solid	19	13 (68)	3 (16)	4 (21)	1 (5)	1 (5)
Anaplastic	48	22 (46)	19 (40)	8 (17)	6 (12 5)	2 (4 2)
Total	211	137 (65)	49 (23 2)	23 (11)	12 (6)	16 (7 6)

* Growth of a tumour either in the thyroid or in the neck i e a lymph node

Table 5

Duration of symptoms Percentages given in parentheses

Length in months	Papillary	Follicular	Solid	Anaplastic	Total
< 3	27 (24)	6 (14)	8 (40)	23 (46)	64 [illegible]
3–12	31 (27)	16 (37)	4 (20)	18 (36)	69 [illegible]
> 12	49 (43)	15 (35)	8 (40)	5 (10)	77 [illegible]
Unknown	7 (6)	6 (14)	0	5 (8)	[illegible]
Total	114 (100)	43 (100)	20 (100)	50 (100)	

The duration of symptoms before diagnosis appears in Table 5 The papillary carcinoma is often regarded as slowly growing However in this material the duration was less than 12 months for 51 per cent of the patients

Signs The clinical findings on palpation of the thyroid gland appear in Table 6 Metastatic cervical lymph nodes were found in 125 patients (55 [illegible]) In the papillary [illegible]

Table 6

Palpation of the thyroid gland in 227 patients Percentages given in parentheses

Thyroid gland	Papillary	Follicular	Solid	Anaplastic	Total
Normal	27 (23 7)	7 (16)	2 (10)	1 (2)	37 (16)
Goitre (diffuse or nodular)	22 (19.2)	9 (?1)	9 (45)	19 (38)	59 (26)
Enlargement of one lobe	28 (24 6)	9 (21)	4 (20)	18 (36)	59 (26)
Adenoma <3 cm	18 (15 8)	12 (28)	3 (15)	3 (6)	36 (16)
Adenoma >3 cm	19 (16 7)	6 (14)	2 (10)	9 (18)	36 (16)

Table 7

Regional node metastases Preoperative findings compared with the operative ones in 78 patients with papillary carcinoma Percentages given in parentheses

Before operation	Operation	
	Metastases	No metastases
Regional nodes	58 (94)	4 (6)
No regional nodes	7 (44)	9 (56)
Total	65 (83)	13 (17)

Table 8

Site of primary metastases (a) and during follow up (b) in 227 patients

Site	Papillary		Follicular		Solid		Anaplastic		Total (a+b)	
	a	b	a	b	a	b	a	b	No	Per cent
Cervical nodes	72	13	16	4	12	4	25	4	150	66
Lungs	12	8	1	2	1	3	9	2	38	17
Bones	3	4	12	1	2	1	1	3	27	12
Liver	0	1	0	1	0	1	0	2	5	2
Brain	0	1	0	1	0	0	0	1	3	1
Skin	0	2	0	1	0	0	0	0	3	1

group 72 patients (64°) had cervical node metastases at the primary examination The difference between the preoperative findings and the frequency of metastatic nodes at operation was high in this group in 7 of 16 patients (44 °o Table 7) the metastases were not diagnosed preoperatively FRAZELL & FOOTE (1958) reported a false negative finding in 62 per cent of 182 patients with papillary carcinoma

Table 9

Paresis of vocal cord in 227 patients

Tumour type	Paresis	
	No	Per cent
Papillary	2	2
Follicular	4	9
Solid	5	25
Anaplastic	21	42
Total	32*	14

* 4 patients had a history of previous surgery of the neck with injury of the recurrent nerve

Table 10

Preoperative evaluation of thyroid scintigraphy in 125 patients

Tumour type	No	Cold tumour		Atypical		Normal	
		No	Per cent	No	Per cent	No	Per cent
Papillary	62	39	63	10	16	13	1[illegible]
Follicular	17	10	59	5	29	2	1[illegible]
Solid	14	9	64	5	36	0	
Anaplastic	32	29	91	3	9	0	
Total	125	87	70	23*	18	15	1[illegible]

* 6 patients had a history of previous surgery of the neck

The frequency of lung metastases at chest radiography was 10 per cent 2 patie only had symptoms in both cases dyspnea

The distribution of metastases at the time of diagnosis and during the follow-u period is summarized in Table 8

Vocal cord paresis was found in 14 per cent (Table 9)

Primary treatment During this period (1960 to 1970) the common surgical procedure was total lobectomy on the tumour side and subtotal lobectomy on the other side followed by extirpation of metastatic nodes (Table 11)

Irradiation was administered as high voltage irradiation 50 to 60 Gy in abo 65 days ^{131}I was given in 2 to 5 doses of 50 to 150 mCi

Therapy with thyroid hormone was given in a few cases without hypothyroid but with local or metastatic disease no effect was evident

Table 11

Primary treatment Percentages given in parentheses

Tumour type	Surgery				^{131}I	Irrad	Irrad $+^{131}I$	None
	Alone	+irrad	$+^{131}I$	+irrad $+^{131}I$				
Papillary	33 (29)	17 (15)	26 (?3)	17 (15)	1	12 (11)	0	8 (7)
Follicular	9 (?1)	4 (9)	11 (26)	1 (2)	13 (30)	0	4 (9)	1 (?)
Solid	4 (20)	7 (35)	1 (5)	0	0	5 (?5)	2 (10)	1 (5)
Anaplastic	8 (16)	12 (24)	8	5 (10)	2 (4)	19 (38)	1 (?)	3 (6)
Total	54 (24)	40 (17)	38 (17)	23 (10)	16 (7)	36 (16)	7 (3)	13 (?)

Table 12

Five year corrected survival according to microscopy and sex

Tumour type	No of cases	Women (per cent)	Men (per cent)
Papillary	94	77	56
Follicular	36	63	46
Solid	19	64	25
Anaplastic	49	14	18
Total	198		

* Including 5 patients who died within 5 years from other causes than thyroid carcinoma

Metastases The distribution of metastases found initially and subsequently in the follow up period (Table 8) correlates well with the findings of FRANSSILA (19[illegible]) who reported on 231 cases However the frequency of metastatic cervical lymph nodes was higher in the present material (55 % at the time of diagnosis) than in his Finnish material (15 %)

Recurrences during the follow up period appeared in 42 patients The time from the diagnosis to the detection of local recurrence regional or distant metastases varied from 6 months to 7½ years except in patients with anaplastic carcinoma where half of the patients developed recurrences within 3 months Only 9 patients had local recurrence compared with 30 patients in FRANSSILA's material All appeared within 3½ years after the primary treatment except in one case in which it [illegible] after 7½ years The mean time from the primary treatment to the recurrence of [illegible] local tumour was less than 2½ years FRANSILA median 1.4 years range [illegible] years present material median 2 4 years range 0 5 to 7½ years Since [illegible] groups are of the same size in the two materials, this difference in local [illegible]

Table 13

5 year crude survival according to stages and microscopy

Tumour type	Stage I		Stage II		Stage III		Stage IV	
	No of cases	Survival (per cent)	No of cases	Survival (per cent)	No of cases	Survival (per cent)	No of cases	Survival (per cent)
Papillary	24	92	35	83	22	41	13	15
Follicular	14	65	7	43	5	60	10	40
Solid	3	67	5	60	8	38	3	0
Anaplastic	13	38	7	0	19	10	10	0
Total	54		54		54		36	

rate could be due to dissimilarity in the primary treatment The only difference in this respect is that of FRANSSILA s patients 35 received ^{131}I either in combination with surgery or external radiation or as the only therapy whereas in the present material 82 patients were treated with ^{131}I

In patients who developed metastases in cervical or in other regions the major of recurrences appeared earlier than 3½ years from the primary treatment, i e in 20 of 25 patients (80 %) with cervical nodes and in 23 of 35 (66 %) with distant metastases

Survival data were obtained by the anniversary method i e information was gathered about each patient on the anniversary of the first examination A total of 198 patients was followed for at least 5 years

The survival rates are corrected survival rates i e corrected for the normal mortality in a population of the same age and sex in Denmark (Table 12)

It is well known that the pathology of the malignant thyroid tumour influences the prognosis for the patient The survival in this material correlates well with the reported by other authors (HIRABAYASHI & LINDSAY 1961 CUELLO et coll 19[illegible] FRANSSILA 1975)

The clinical stage of the patients (Table 1) influences the prognosis (Table 13). Other factors considered to influence the prognosis are sex and age (HALNAN 19[illegible]). In this material age and to a lesser degree sex seems to influence the survival (Details will be published later)

Autopsy Additional information about the sites of metastases was obtained at autopsy in 50 patients representing 49 per cent of deaths among 102 patients

Pulmonary metastases appeared in 18 of the autopsy cases (Table 14). No metastases had been found on chest films of 8 of these patients 1 6 7 8 8 10 1[illegible] and 44 weeks before death The value of conventional chest radiography performed with the technique used in this material i e p a and lateral exposures with an FSD of 150 cm and 60 kV thus seems to be limited

Table 14

Site of metastases at autopsy 50 patients

Site	Per cent	Papillary (17 cases)	Follicular (8 cases)	Solid (3 cases)	Anaplastic (22 cases)
Local	48	4	4	1	15
Cervical nodes	20	4	1	0	5
Distant nodes	14	2	0	0	5
Liver	16	1	0	2	5
Lungs	36	6	2	2	8
Bones	12	1	1	0	4
Adrenals	6	1	1	1	0
Spleen		1			
Heart		1			
Cardia		1			
Brain				1	
Pericardium					1
No tumour	12	5	1		

Discussion

Thyroid carcinoma varies greatly regarding natural history grade of malignancy and response to treatment The distinction of thyroid carcinoma into papillary follicular medullary and anaplastic carcinoma is clinically and pathologically rational a separation into differentiated and undifferentiated carcinomas should be avoided since this distinction does not reflect the differences in natural history and therapeutic possibilities

The etiologic factors are only partially known Previous irradiation of the neck seems to be a definite factor in inducing neoplasia in the thyroid gland The thyroid region had been irradiated in at least 7 per cent of the present patients 10 to 16 years before the carcinoma was diagnosed The proportion of the population which has received irradiation of the neck in childhood or youth for benign disease is not known but is considered to be less than one per cent

An excessive TSH secretion may stimulate the growth of thyroid neoplasms This has been shown to be the case in animals (DONIACH 1970) Measurement of TSH was not common practice until two years ago at this hospital and consequently the TSH concentration in the peripheral blood could not be evaluated

Metastases to the cervical nodes are a frequent and early finding In this material 125 patients (55) had cervical metastases at their first examination An additional 25 patients (11 %) developed cervical metastases in the follow up period These figures emphasize the importance of the fact that the primary surgery should involve search for and removal of metastatic cervical nodes

Growth of a pre-existing goitre is a typical first symptom in patients with follicular and anaplastic thyroid carcinoma this was also observed by FRANSSILA

(1971) and suggests that the follicular and anaplastic carcimomas may be preceded by a benign disease of the thyroid gland

Besides the history and the palpation of the patient s neck thyroid scintigr[illegible] using $^{99}Tc^{m}$ or ^{131}I gives information about the character of a tumour in the thyr[illegible] gland Scintigraphy was performed in 125 patients (Table 10) Approximately [illegible] per cent of the scintigrams indicated potential malignancy Normal scintigra[illegible] occurred mainly in the papillary group Tumour in the thyroid gland of less than [illegible] carcinoma in a lateral cervical cyst metastasis to a cervical node without dete[illegible] of the primary thyroid tumour or carcinoma of an accessory thyroid at the b[illegible] the tongue were demonstrated

The principles for the treatment of the different types of thyroid carcinoma h[illegible] not been *randomized at any centre Thus the treatment varies from hospital t[illegible]* hospital according to the experience and the traditions Primary surgery cons[illegible] of total or subtotal thyroidectomy combined with extirpation of metastatic cervi[illegible] nodes seems to be important ^{131}I is an excellent agent against certain malig[illegible] thyroid cells This nuclide is almost exclusively concentrated in the thyroid [illegible] in tumour tissue developed from this gland The side effects and sequelae do [illegible] appear to be serious Bone marrow depression even after high doses of [illegible] infrequent Subsequent infertility in patients treated by several hundred mCi d[illegible] not seem to be unavoidable However published reports are rare and include o[illegible] few patients (SARKAR et coll 1976) The experience at this hospital indicates th[illegible] high doses of ^{131}I may depress for several years further growth of even widespr[illegible] metastases especially if these take up iodine

Chemotherapy of thyroid carcinoma does not seem to have improved th[illegible] prognosis However Adriamycin has in a few cases caused regress of tumo[illegible] patients with widespread metastases (GOTTLIEB & STRATTON HILL 1974)

Since survival is correlated to the microscopic type and the clinical sta[illegible] important that the hospitals at which the treatment and the control of patients [illegible] *thyroid carcinoma are centralized attempt to acquire* uniform pathologic cla[illegible] tion and uniform staging in order to compare treatment results from one Cent[illegible] another The histologic grading at this hospital (Table 1) follows the recommenda[illegible] given by the Armed Forces Institute of Pathology However some objectio[illegible] this staging may be raised There is no difference in the prognosis betw[illegible] and II in the papillary group and the evaluation of distant metastases was ma[illegible] from pulmonary and skeletal radiography In the future this examination [illegible] to be supplemented with iodine whole body scintigraphy or $^{99}Tc^{m}$ labelled pol[illegible] pyrophosphate bone scintigraphy which often are more sensitive than conve[illegible] radiography (O MARA 1974)

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SUMMARY

The natural history and the clinical findings in 227 patients with thyroid carcinoma are described and the etiology discussed The need for uniform pathologic classification and staging is emphasized

ZUSAMMENFASSUNG

Der Krankheitsverlauf per se und die klinischen Befunde von 227 Patienten mit Thyreoideakarzinom werden beschrieben und die Atiologie diskutiert Die Notwendigkeit einer gleichformigen pathologischen Klassifikation und Stadieneinteilung wird hervorgehoben

RESUME

L auteur décrit l histoire naturelle et les signes cliniques observes chez 227 malades atteints de carcinome thyroidien et en discutent l etiologie Ils insistent sur la nécessite d une classification anatomopathologique uniforme et d une classification en stades

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EN BLOC IRRADIATION OF TUMOURS OF THE HEAD AND NECK AND THEIR LYMPHATICS

II Early results and side effects

T ANDERSSON A BJÖRKLUND T LANDBERG C MERCKE
and G SVAHN TAPPER

A technique for en bloc irradiation of tumours of the head and neck and their lymphatics using ^{60}Co and 8 MV roentgen rays has recently been described (LANDBERG & SVAHN TAPPER 1976) This technique is a multi field treatment allowing for a high radiation absorbed dose in both the primary tumour and its regional lymph nodes in the neck without exceeding the tolerance dose of organs at risk such as the spinal cord The report included a description of patient immobilization dose planning simulation and surveyance of treatment The dose distributions for the first 68 patients who received a full treatment were analyzed

The early treatment results and the side effects are now reported in the 68 patients who concluded the radiation and in 6 who discontinued the treatment

Material and Methods

The material included 74 patients with primary malignant tumours of the head and neck region who were treated with the new technique during the years 1971 to 1975

The site of the primary tumour was the nasopharynx in 10 patients the hypo

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pharynx in 19 the larynx in 10 the thyroid gland in 18 17 patients had miscellaneous tumours mainly of the oral cavity

The lesions had been classified according to the TNM system of UICC (19 No patient had distant metastases at the time of treatment

The radiation therapy was combined with major surgical procedures in these 23 patients The irradiation was given before surgery in 3 patients following surgery in 18 and 2 patients received irradiation both before and after the operation

In 22 patients chemotherapy was given and then mainly for relapsing disease

The patients were followed regularly The follow up was concluded on 1 January 1976 and had then ranged from 1 to 5 years

Radiation side effects were divided into early effects and late effects The early side effects were recorded as mucositis dryness of the mouth skin reactions (e g erythema or moist epidermitis) impaired food intake and others Late side effects were divided into dryness of the mouth dental decay osteonecrosis induced by radiation fibrosis of normal connective tissue skin reactions (e g cutaneous atrophy or ulceration) and others For both early and late reactions a 4-grade scale was used where 0 = no detectable reaction + = normal radiation side effect + + = more marked but during the follow up clinically reversible side effect and + + + = marked and irreversible side effect (e g necrosis)

For each patient the minimum radiation absorbed dose in demonstrated tumour had been calculated as well as the maximum target absorbed dose For each patient the cumulative radiation effect (CRE) was calculated for these 2 *absorbed dose* values Most treatments had been given in 2 series with two thirds of the total absorbed dose in the first series and an interval of 4 to 5 weeks between the two series When calculating the CRE gap correction according to KIRK et coll (1975) was used

Conclusions about the results of treatment could only be drawn regarding tumours of the nasopharynx and tumours of the hypopharynx *In other* sites the results did not at the time of follow up lend themselves to a meaningful analysis for several reasons such as heterogeneity of the patient material or of types of combinations of different treatment modalities or due to too short follow up All 74 patients were suitable for the analysis of the radiation side effects

Clinical data for all patients are given in Table 1

Tumours of the nasopharynx Ten patients had a nasopharyngeal tumour 5 males and 5 females the ages ranged between 26 and 72 years with a mean of 55

Seven patients had anaplastic carcinoma and 3 poorly differentiated squamous cell carcinoma

Five of the tumours were classified as T1 and 5 as T2 *and the* nodal status was N0 for 2 patients N1 for 2 N2 for 3 and N3 for 3 patients

Tumours of the hypopharynx occurred in 19 patients 17 males and 2 females the ages ranged between 54 and 83 years with a mean of 66

Table 1

Distribution of sex age and TNM stage in 74 patients All patients were in M 0 stage

Site	No of cases	Males	Females	Age (range and mean)	TNM								
					T0	T1	T2	T3	T4	N0	N1	N2	N3
Nasopharynx	10	5	5	26–72 (55)	—	5	5	—	—	2	2	3	3
Hypapharynx	19	17	2	54–83 (66)	—	3	7	5	4	12	2	4	1
Larynx	10	9	1	47–73 (60)	—	—	4	3	3	5	4	1	—
Thyroid	18	10	8	16–80 (58)	—	—	6	5	7	9	4	5	—
Miscellaneous tumours of the oral cavity	17	13	4	25–76 (68)	2	3	1	5	6	9	3	1	4

One patient had an anaplastic carcinoma and 17 squamous cell carcinoma which was poorly differentiated in 3 and moderately or well differentiated in 14 In one patient only cytologic examination of a lymph node metastasis was performed which revealed necrotic carcinoma

Three of the tumours were classified as T1 7 as T2 5 as T3 and 4 as T4 The nodal status was N0 for 12 patients N1 for 2 N2 for 4 and N3 for 1 patient

Tumours of other sites Ten patients had carcinoma of the larynx 18 carcinoma of the thyroid and 17 miscellaneous tumours of mainly the oral cavity For all these 45 patients the tumours were classified as T0 in 2 instances as T1 in 3 as T2 in 11 as T3 in 13 and as T4 in 16 and the nodal status was N0 for 23 patients N1 for 11 N2 for 7 and N3 for 4 patients Thus these patients generally had advanced tumours

Results and Discussion

Early treatment results

Tumours of the nasopharynx The radiation therapy was concluded in all 10 patients The minimum radiation absorbed dose in demonstrated tumour was 61 Gy given in 36 fractions during 90 days split course all mean values

In all 10 patients a complete regression of the nasopharyngeal tumour was obtained In 7 of the 8 patients with palpable neck metastases a total regression of the neck masses occurred whereas in 1 the enlarged nodes persisted A neck dissection was performed in this patient

Four patients are alive with no evidence of disease at 24 26 27 and 29 months respectively after treatment Four have died after 13 13 22 and 44 months respectively with distant metastases but no local recurrence and 2 patients have died after 14 and 19 months respectively with distant metastases and local recurrence

In 5 of the patients distant metastases were the first new indication of disease and

were diagnosed 9 to 40 (mean 17) months after the beginning of the treatment [illegible] one patient a local recurrence was the first new sign of disease being di[illegible] after 6 months

Three of the 4 patients alive without evidence of disease had initially lymph node metastases In 2 of them the nodal status was classified as N1 and in the third [illegible] N2 The follow up for these 3 patients is 24 26 and 29 months respectively

Six of the 10 patients have had distant metastases which were diagnosed [illegible] to 40 (mean 17) months

Radiation therapy is considered to be the method of choice in the treatment of malignant tumours of the nasopharynx Recently 3 large patient series have been reported (WANG & MEYER 1971 LEDERMAN 1975 HOPPE et coll 1976) WANG & MEYER found that patients without regional metastases had an overall 5 year survival rate of 54 per cent whereas patients with unilateral lymphadenopathy had a survival rate of only 38 per cent In the series of LEDERMAN the corresponding values were 46 and 18 per cent respectively Thus the occurrence of regional lymph node metastases has a significant influence on the survival and it would seem to be prefer[illegible] to treat the lymph nodes in the neck before metastases are detectable an opinion which is supported by the report of HOPPE et coll They found prophylactic irradiation of the neck always to be successful if the primary site was controlled The anatomic distribution of these regional lymph nodes has been explored by LINDBERG (1972) He found that the upper parts of both the deep and the posterior cervical lymph nodes had the highest incidence of metastases These nodes as well as practically all other lymph nodes in the neck and the supraclavicular fossae are incl[illegible] in the target volume with the technique used in the present series

Of the present 10 patients 8 were locally symptom free in the nasopharynx and the cervical lymph nodes but 6 relapsed at distant sites Distant failure also dom[illegible] in the series of HOPPE et coll but their patients also had a high frequency [illegible] of local failure

The technique used in the present series resulted in a good cure rate in the nasopharynx and cervical lymph nodes The main obstacle for cure was distant metastases which occurred within 2 years This length of interval was considered by LEDERMAN to be critical for the evaluation of treatment of tumours of the nasopharynx [illegible] thus though the follow up averaged only 17 months in the present series, it may be concluded that the irradiation used is sufficient for achieving acceptable local c[illegible] However there may be a need for systemic treatment of occult distant metastases

Tumours of the hypopharynx The radiation therapy was concluded in 17 pa[illegible] but discontinued in 2 because of poor general condition Patients who concluded treatment received a minimum radiation absorbed dose in demonstrated tumour [illegible] mean 60 Gy given in mean 34 fractions over mean 82 days split-course

Nine patients had a total regression of all demonstrated disease Three had T1 tumours 4 had T2 1 had T3 and 1 had T4 and the nodal status was N0 [illegible]

Table 2

Number of patients with early and with late radiation side effects of marked character

		Marked late radiation side effects	
		Yes	No
Marked early radiation side effects			
Yes	40	13	27
No	34	1	33
Total		14	60

patients Two of the 9 patients with complete remission are alive without evidence of disease at 42 and 45 months respectively after treatment and one is alive with a local recurrence (follow up 22 months) whereas 6 have died after mean 24 months all 6 with a local recurrence and 2 of them also with distant metastases

Ten patients had only a partial remission all 10 have died after mean 9 months one of them also having distant metastases

Distant metastases thus occurred in 3 of the 19 patients and they were diagnosed after 10 11 and 14 months respectively

A neck dissection was performed in one patient otherwise surgery was not applied

In the present series irradiation was used as the treatment of tumours of the hypopharynx Most tumours were of moderate or advanced size at diagnosis On the other hand a relatively low frequency of regional lymph node metastases was encountered Further distant metastases occurred in only a few cases

The early results indicate a fair local response initially after radiation therapy since all tumours showed a regression of varying degree However most patients died within 2 years and then above all because of a local recurrence at the site of the primary tumour or in the cervical lymph nodes

Since failures occur early in carcinoma of the hypopharynx a relatively short follow up may be adequate for evaluation of the treatment results

Figures for results of therapy in carcinoma of the hypopharynx vary widely in the literature and it is difficult to get a representative impression of the value of different therapeutic modalities Most reports are not based on prospective controlled series and a breakdown into subgroups of stage and type of therapy usually gives such small materials that general conclusions are not warranted However it is apparent that radiation therapy alone usually only offers a short lasting remission and cures are usually reported to be unusual Thus CARPENTER et coll (1976) reported a 5-year survival rate of only 4 per cent after radiation therapy alone

Apparently a more aggressive therapeutic approach is needed in order to improve the results FLETCHER & JESSE (1977) found a reduction in local recurrence rate from

Table 3

Radiation absorbed dose number of fractions and number of days for patients with and [illegible] and late radiation side effects

	Early radiation side effects		Late radiation [illegible]	
	Normal	Marked	Normal	[illegible]
Absorbed dose (Gy)				
Maximum target absorbed dose				
Range	29–76	30–81	29–81	[illegible]
Mean	64	66	65	65
SD	9	8	9	6
Minimum absorbed dose in demonstrated tumour				
Range	23–64	26–68	23–69	46–65
Mean	55	56	56	56
SD	9	9	9	7
Number of fractions				
Range	12–41	15–43	12–41	[illegible]
Mean	32	33	32	34
SD	6	5	5	5
Number of days				
Range	17–153	21–1[illegible]6	21 153	[illegible]
Mean	80	81	79	[illegible]
SD	24	18	21	18

35 per cent for radiation therapy alone to 11 per cent with a combination of [illegible] and irradiation They recommended a relatively restricted surgery followed [illegible] radical irradiation

Carcinoma of the hypopharynx is a deleterious disease and today no [illegible] way to improve the results is visible

Radiation side effects

Early radiation side effects of marked degree (grades [illegible] or [illegible]) were [illegible] served in 40 of the 74 patients (Table 2) the remaining 34 having no or [illegible] (grades 0 or +) side effects Twenty three of the 40 had more than one [illegible] Marked mucositis occurred in 14 patients a very dry mouth in 5 moist [illegible] in 5 and impaired food intake in 22

In 6 patients the treatment had to be discontinued most often due to early [illegible] effects in old and debilitated patients

Late radiation side effects of marked degree (grades [illegible] or [illegible]) occurred [illegible] 14 patients Ten experienced a very dry mouth 2 had abnormal dental [illegible] 4 had soft tissue fibrosis No instance of skin ulceration and no case of [illegible] myelopathy occurred

Table 4

CRE-values for patients with and without early and late radiation side effects

	Early radiation side effects		Late radiation side effects	
	Normal	Marked	Normal	Marked
Number of patients	34	40	60	14
CRE value of				
Maximum target absorbed dose				
Range	1 170–1 990	1 120–2 130	1 120–2 130	1 460–1 960
Mean	1 700	1 750	1 750	1 700
SD	250	176	174	135
Minimum absorbed dose in demonstrated tumour				
Range	930–1 700	970–1 880	930–1 880	1 080–1 800
Mean	1 500	1 550	1 550	1 500
SD	169	174	172	190

When treating a nasopharyngeal tumour care has to be taken to avoid radiation effects in the eyes optic fascicles (DESCHRYVER et coll 1971) brain stem and pituitary gland Such radiation side effects did not occur in the present series

The correlation between the occurrence and non-occurrence of early and late radiation side effects respectively appears in Table 2 Of the 40 patients with marked early reactions 13 also had marked late reactions Of the 34 without marked early reactions 1 later had a marked late reaction (dental decay due to xerostomia)

An analysis was carried out to see if there were any particular characteristics about the patients who developed marked early or late radiation side effects

In an area like the head and neck it may often be difficult to establish precisely if a reaction is a pure radiation reaction of normal tissue Radiation reactions of the tumour infection and poor food intake may also play a role Further the premorbid condition of the mucosal lining and the connective tissue also play a role a factor which has long since been established The age of the patient may also be assumed to play a role due to less perfect regenerative capacity in high age and a more strained circulation

The relation between side effects and absorbed dose number of fractions and number of treatment days was analyzed (Table 3) The maximum target absorbed dose and the minimum absorbed dose in demonstrated tumour were chosen for this analysis since their distribution corresponds well with the region of radiation reactions The largest absorbed dose value was taken as the maximum provided its isodose included an area of at least 2 cm in a section The minimum value represents an absolute minimum in demonstrated tumour The size of the target volume only varied little in the present series and all patients were treated with the method described From Table 3 it appears that no separation between the occurrence and the

Table 5

Age of patients with and without marked early and late radiation side effects

	Marked early radiation side effects		Marked late radiation side effects	
	Yes	No	Yes	No
Range	26–83	16–80	47–76	16–83
Mean	63	61	69	60
SD	12	13	7	13

non occurrence of side effects could be demonstrated only on the basis of absorbed dose and fractionation However the analysis includes 6 patients in whom treatment was discontinued mainly due to side effects These patients only received low absorbed doses and thus to some extent bias the analysis

For each patient a calculation of the CRE value for the absorbed dose levels given in Table 3 was performed The CRE values for groups with and without early and late radiation reactions respectively appear in Table 4 No correlation between CRE values and radiation reactions was found

The CRE concept (KIRK et coll 1971) is based on the NSD concept (ELLIS 1969) The derivation of the NSD concept allows for its use for comparison between different fractionation schedules and different absorbed dose levels with respect to one radiation reaction namely late necrosis of normal connective tissue KIRK et coll stated that the CRE concept could also be used for comparison of different kinds of normal radiation effects on connective tissue up to and including necrosis In the present series no case of late necrosis of normal connective tissue was found and thus the use of the NSD concept (and CRE-concept) according to the original definition laid down by ELLIS is not warranted Nor could a separation on the basis of CRE values be found when considering late reactions other than necrosis or when considering early reactions

The age of the patient may be considered to be of importance Patients with late reactions were somewhat older than those without (Table 5) but for early radiation reactions no age difference could be demonstrated

The site of the tumour seems to be of importance for the occurrence of reactions (Table 6) Early reactions were particularly common in patients in which the tumour was located to the food passages (oral cavity and hypopharynx) Late reactions did not show any clear trend

Surgery did not seem to be an important factor for the development of marked radiation side effects since of 40 patients with early such effects in only 8 had [illegible] surgery been performed and of 14 with late such effects only 2 had been operated upon

Table 6

Frequency of marked early and late radiation side effects for different tumour sites Each number denotes number of patients

Tumour localization	No of patients	Marked early radiation side effects		Marked late radiation side effects	
		Yes	No	Yes	No
Nasopharynx	10	5	5	3	7
Hypopharynx	19	14	5	5	14
Larynx	10	3	7	0	10
Thyroid	18	6	12	3	15
Oral cavity	17	12	5	3	14
Total	74	40	34	14	60

Early and late reactions after radiation therapy of tumours of the head and neck often represent complex effects It is usually not a simple task to sort out what quality or quantity of reactions that depend only on the ionizing radiation and which role other factors such as tumour reaction effects of surgery and infection may play In the present series reactions of clinical importance were particularly frequent in patients who had tumours of the oral cavity and the hypopharynx The size of the total absorbed dose in the range used probably also plays a role even though this could not be demonstrated in the present series which only had a limited range of this parameter Also the CRE values did not give a separation between patients with and without reactions

The present series illustrates a common difficulty in the evaluation of tissue tolerance since patient series when other parameters are comparable usually differ only little as regards radiation absorbed dose and fractionation

SUMMARY

The results and side effects of en bloc irradiation of ear nose and throat tumours and their lymphatics showed that the technique had been successful in nasopharyngeal carcinoma but poor in carcinoma of the hypopharynx Marked early and late radiation side effects were relatively common in high age and with certain tumour sites whereas no correlation could be demonstrated with total absorbed dose fractionation cumulative radiation effect or major surgery

ZUSAMMENFASSUNG

Die Ergebnisse und Nebeneffekte einer en bloc Bestrahlung von Ohren Nasen Hals-Tumoren und deren Lymphgefasse zeigte dass die Technik erfolgreich beim Nasopharynx Karzinom ist jedoch wenig erfolgreich beim Karzinom des Hypopharynx Ausgepragte fruhzeitige und spate Strahlennebeneffekte waren relativ gewohnlich bei hohem Alter und bei gewisser Tumorgrosse wahrend keine Korrelation zur gesamtabsorbierten Dosis der Fraktionierung dem kumulativen Strahleneffekt oder umfassender Chirurgie gefunden werden konnte

RESUME

Les résultats et les effets secondaires de l irradiation en bloc de tumeurs oto-rhino-laryngologiques et de leurs lymphatiques ont montre que cette technique a été efficace dans le carcinome naso pharyngien mais a donne de mauvais resultats dans le carcinome de l'hypopharynx Les effets secondaires précoces et retardés des radiations ont été relativement fréquents chez les sujets d age éleve et dans certains sieges de tumeurs alors qu on ne peut pas mettre en evidence de corrélation avec la dose absorbée totale le fractionnement, l'effet cumulatif de l irradiation ou une chirurgie majeure

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RADIATION RESPONSE MODIFIED BY DEGRADABLE STARCH MICROSPHERES

Experiments on the rat s foot

J O FORSBERG B JUNG and B LARSSON

Dissolved molecular oxygen enhances the effect of ionizing radiation with low linear energy transfer (LET) (cf VAN DEN BRENK 1969) In radiation therapy this oxygen effect is encountered in all well-oxygenated tissues while diminished tissue oxygen tension in malignant tumours invokes partial protection to radiation The possibility of attaining tissue protection in single-dose irradiation through temporary local hypoxia has been experimentally investigated in rats by intraarterial injection of cross-linked starch microspheres 40 μm in diameter The spheres obstruct the blood flow at the level of the arterioles and are degraded by endogenous blood amylase As a model the rat s hind foot was used Scoring followed a grading scale based on characteristic indices of skin injury

Preliminary experiments suggested that a very profound hypoxia could be attained during similar experimental circumstances (ARFORS et coll 1976)

Material and Methods

Animals Sprague Dawley male rats weighing about 300 g and bred on a standard diet were used The animals had free access to food and water before and after the experiments After irradiation the animals were kept in separate cages

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Table 1

Maximum skin reaction in the non protected group as function of dose n = the total number of evaluated feet in each sub group For definition of skin reaction see Fig 3

Skin reaction	Dose (Gy)					
	17 5	20	22 5	25	27 5	30
6	—	—	1	6	3	5
5	—	—	8	10	3	—
4	—	—	3	4	—	—
3	—	—	5	2	—	—
2	—	—	9	5	—	—
1	3	3	6	1	—	—
n	3	3	32	28	6	5

Table 2

Maximum skin reaction in the protected group as function of dose n = the total number of evaluated feet in each sub-group For definition of skin reaction see Fig 3

Skin reaction	Dose (Gy)					
	35	40	45	50	55	60
6	—	1	2	3	3	3
5	—	—	1	14	—	—
4	—	1	3	2	—	—
3	—	—	—	—	—	—
2	1	4	12	1	—	—
1	2	4	2	1	—	—
n	3	10	20	21	3	3

In the protected (P) group of feet a suspension of degradable microspheres wa[illegible] injected through an indwelling catheter In the non protected (NP) group physiol[illegible] saline was injected Each animal was given P mode treatment in one foot and NP mode in the other foot Both groups were divided into six subgroups wh[illegible] irradiated with graded doses The choice of dose in the 12 groups was based on the results of a preliminary series indicating a dose modification factor of 0.5 Th[illegible] the P feet were given doses higher than the corresponding NP feet by a fa[illegible] (Tables 1 2) For each foot the dose and group (P or NP) were decided at ra[illegible] Seven feet were left unirradiated for control

The starch microspheres had a diameter of 40 μm and were used at a concen[illegible] of 80 mg/ml (7 2 10^5 spheres per ml) in saline The rate of degradation depe[illegible] on the degree of cross linking of the starch molecules In vitro half lives of th[illegible]

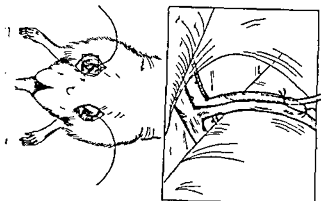


Fig 1 Indwelling catheters in the groins detail of catheter position in branch of the femoral artery

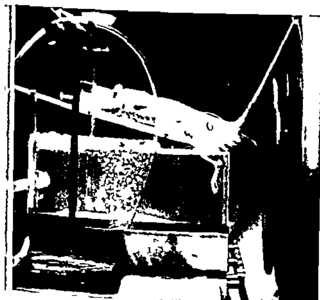


Fig 2 Rat in position for irradiation hind feet hanging down in water bath

particles were 20 and 10 min in 20 ml buffered saline with 240 and 1 500 IU standard amylase respectively (NYBERG 1976)

Blood flow measurements demonstrated (FORSBERG 1978) that the flow in the foot was negligible during a period of about 10 min after injection of 1.8×10^6 of the starch microspheres Subcutaneous pO in the blocked foot (measured with an oxygen needle electrode IBC Differential Oxygen Analyser) declined almost to zero during the blocking period and then rapidly returned to the original level

Anesthesia The treatment including operation of each single animal lasted about 30 min and was carried out under intraperitoneal Mebumal sodium anesthesia (60 mg/ml–40 mg/kg) given 20 min before irradiation

Operative techniques After incision in the groin a branch from the femoral artery was dissected and ligated 15 mm distally to the femoral artery (Fig 1) Under a dis

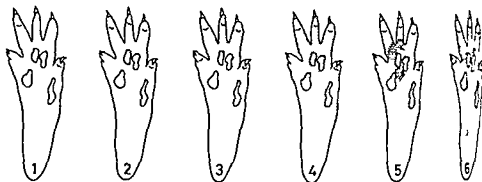


Fig 3 Degrees of skin reaction used for evaluation 1 = Slight epidermitis of one toe or corre[illegible] sponding area in the sole 2 = Dry epidermitis of more than one toe but no epidermitis in the sole 3 = Dry epidermitis of more than one toe plus the distal part of the sole 4 = Severe dry epider[illegible] mitis and oedema including all toes and a large part of the sole 5 = Moist epidermitis in a small area often situated at the base of the toes or centrally in the sole 6 = Severe moist epidermitis including the toes and a large part of the sole often proceeding into a larger necrosis.

section microscope the branch was incised and catheterized in a retrograde direct[illegible] with a PP 10 catheter (Portex) the tip of which had been tapered to a diameter of about 160 μm The catheter was filled with heparinized saline (500 IU Hep[illegible] Vitrum + 100 ml NaCl 0 9 %) and the tip was advanced into the artery branch to a point about 3 mm from the entrance into the femoral artery The same procedur[illegible] was carried out in the other groin

With the animal placed on its back 0 25 ml of the used microsphere suspens[illegible] (a total of 1 8 × 10^6 spheres) or alternatively 0 25 ml of saline was injected Whe[illegible] (for P feet) the foot became quite pale (about 30 s after injection) the animal was placed in the abdominal position on a plexiglass bridge placed over a 15 cm × 15 cm × 27 cm plexiglass box with 3 mm thick walls into which the hind feet were allowed to hang down (Fig 2) The box was filled with 27 C water circulated from a ther[illegible] stated reservoir In order to keep a low oxygen content in the water N_2 was bub[illegible] through the radiation box The bridge was placed obliquely 15 toward the hor[illegible] zontal plane in order to avoid irradiation of the trunk The feet then hung practica[illegible] parallel to the posterior wall of the box which was oriented at right an les to the horizontal beam of radiation

The foot position could easily be controlled through the wall attention bein paid to its distance from the posterior wall of the box (15 mm) as well as to its positi[illegible] the field which was light indicated Five min after injection of the microsp[illegible] or saline the irradiation was started

Irradiation A linear accelerator (M E L SL 75 Super) was used (8 MV [illegible] rays 600 pulses/s pulse length 0 2 μs dose rate 16 Gy/min) The irradia[illegible] fie[illegible] measured 2 4 cm × 4 2 cm in cross section and covered the whole foot up to a p[illegible] above the heel Dose buildup was provided by 3 mm plexiglass and 15 mm [illegible]

Table 3

Mean latency period (days) for various skin reactions irrespective of radiation dose Figures within parentheses give percentage of first observation of a certain skin reaction within ±1 day from the mean value

Skin reaction	Non protected	Protected
1	8 (75)	8 (80)
2	8 (74)	9 (68)
3	10 (69)	8 (75)
4	10 (81)	10 (73)
5	12 (73)	12 (86)
6	12 (77)	12 (92)

The source to skin distance was 60 cm The dose non uniformity over the foot was small (±2) The uncertainty in dose delivery from foot to foot was estimated to be ±2 per cent mainly depending on possible distance differences

Immediately after irradiation it was ascertained that the feet of the P group still were quite pale The catheters were then removed the artery branches ligated with 5-0 silk and the skin incisions stitched

Evaluation of skin reaction FOWLER et coll (1972) used mice feet in experiments designed to compare the effects of irradiation with roentgen rays and neutrons In principle the same technique of evaluation was used here but the scoring system was modified according to Fig 3 The feet were observed each afternoon for 28 days After this period observations were made twice during another 10 days All observations were made by the same individual

Due to technical difficulties with the thin catheters 17 of the P feet had to be excluded from the experiment Out of 81 animals 4 died within one day from anesthesia complications No spontaneous deaths occurred among the remaining animals

Statistics The dose for 50 per cent incidence of the different skin reactions was determined by probit analysis (BEYER 1968) The two parameters in the error function were determined by weighted least squares techniques and their uncertainties by matrix inversion All calculations were made on a table top calculator (Hewlett Packard 9820)

Results

During the first few days hyperemia and vascular hyperreflexia of the foot skin were seen in both groups disappearing within 4 days The typical epidermic reaction usually appeared on the 7th to 8th day (Table 3) For the final evaluation re

Table 4

Mean latency period (days) for various skin reactions as function of absorbed dose Figures within parentheses give percentage of first observations of a certain skin reaction within ±1 day from the mean value

Dose (Gy)	Skin reaction		
	1+2	3+4	5+6
Non protected			
17 5	8 (100)	—	—
20	8 (100)	—	—
22 5	8 (69)	10 (69)	13 (82)
25	8 (74)	10 (76)	12 (71)
27 5	8 (75)	10 (100)	12 (100)
30	7 (100)	10 (100)	11 (100)
Protected			
35	8 (100)	—	—
40	8 (67)	9 (100)	10 (100)
45	9 (58)	11 (43)	11 (100)
50	8 (70)	9 (67)	12 (89)
55	7 (100)	10 (66)	11 (100)
60	7 (100)	10 (50)	11 (100)

Table 5

Doses (±95 confidence limits Gy) for 50 per cent incidence of skin reactions of various severity and corresponding dose modification factor DMF (±95 confidence limits)

Skin reaction	Non protected	Protected	DMF
≥6	26 8 ±1 18	53 79±4 10	0 50±0 03
≥5	24 18±0 82	47 37±1 50	0 51±0 0[illegible]
4	23 44±0 78	45 67±1 68	0 51±0 0[illegible]
3	22 62±0 94	45 12±1 96	0 50±0 0[illegible]

mained 77 feet in group NP and 60 feet in group P (Tables 1 2) All feet in the [illegible] had at least a slight skin reaction The degrees 1 and 2 often passed quickly a [illegible] thus difficult to determine Reactions of higher degrees were observed with [illegible] frequency but were readily scored (Tables 1 2) No significant difference was [illegible] between P and NP feet with respect to time of appearance of varying degrees of epidermitis (Table 3) or to different doses (Table 4)

When severe irradiation damage (degree 6) was observed the animals (n [illegible] were immediately killed The remaining animals were all observed to heal com[illegible]

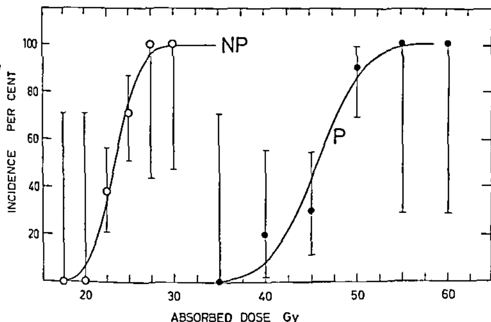


Fig 4 Positive skin reaction of protected (P) and non protected (NP) feet reaching degree 4 or higher versus absorbed dose The bars represent 95 per cent confidence limits Within given limits of uncertainty similar results were obtained for degrees 3–6 of skin reaction (cf Tables 1 and 5)

during 5 weeks after irradiation The results of the observations of skin reaction on the feet are given in Table 5 In the two groups the dose causing effect in 50 per cent of the animals was calculated for the four highest degrees of reaction The modification factor as seen in the table was nearly the same 0 5 for the four degrees The dose-effect curve for degree 4 appears in Fig 4

Concomitant with the skin reaction loss of hair was observed (Fig 5)

Discussion

The present results and measurements of oxygen tension and blood flow in the rat s foot (Forsberg) support the findings by Arfors et coll that almost total hypoxia could be achieved in the intestine of the pig after blockade of the blood flow with starch microspheres

The spheres were easily administered Ischemia appeared quickly and during the phase of degradation rapidly disappeared again Starch is degraded by blood serum amylase (in the rat about 6 000 IU/l) the concentration of which near the blocking spheres determines the rate of degradation and hence the blocking time No indication of toxicity or other complications was observed from the microspheres

Irradiation was performed during the period when according to previous measurements the oxygen tension and the blood flow in the foot were expected to be close

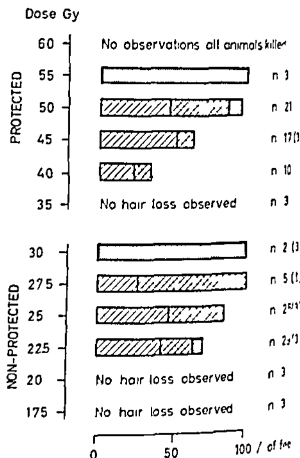


Fig 5 Observations of hair loss in protected and non protected feet as functions of dose n = number of feet observed Within parentheses the number of feet excluded due to severe necrosis in one of the two irradiated feet in an animal ▭ Slight diffuse or local hair loss ▭ Strong diffuse or multifocal hair loss ▨ Subtotal hair loss

to zero The water surrounding the foot probably did not contribute oxygen in sufficient amount to influence the modification factor The effect of radiation may be dependent on tissue temperature As the subcutaneous temperature in the feet of the anaesthetized animals was found to be 27 C this temperature was chosen for the water bath

The oxygen effect is a well known phenomenon in radiation biology The oxygen enhancement ratio (OER) normally observed is 2 to 3 corresponding to a dose modification factor of 0 5 to 0 3 The factor of 0 5 in the present series is ascribed to the protective effect of hypoxia induced by the circulation blockade (OER ~ 2 0) Protection of internal organs by the principles outlined is now under evaluation (Forsberg & Jung 1978 Forsberg et coll 1978 a b)

Acknowledgements

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SUMMARY

Skin reaction in the rat s foot was used as an experimental method to evaluate the protec -ive potential of profound temporary hypoxia against roentgen radiation produced by a -inear accelerator Hypoxia was induced by intraarterial injection of degradable starch microspheres The irradiation dose needed to evoke a certain reaction in the hypoxic feet was 2 0 times the dose giving the same reaction in a control group The results point towards a new technique of inducing local hypoxia in healthy tissues which need to be protected in an irradiation field

ZUSAMMENFASSUNG

Die Hautreaktion des Ratten Fusses wurde als eine experimentelle Methode verwendet um das schutzende Potential einer weitgehenden zeitweiligen Hypoxie gegen Rontgen strahlen von einem Linear Accelerator festzustellen Hypoxie wurde durch intraarterielle Injektion von abbaubaren Starkemikrospharen hervorgerufen Die notwendige Strahlen dosis um eine gewisse Reaktion im hypoxischen Fuss hervorzurufen war das Doppelte der notwendigen Dosis um die gleiche Reaktion bei der Kontrollgruppe hervorzurufen Die Ergebnisse weisen auf eine neue Technik hin lokale Hypoxie im gesunden Gewebe hervorzurufen welches in einem bestrahlten Feld geschutzt werden soll

RESUME

Les reactions cutanées de la patte du rat ont ete utilisees comme methode expérimentale pour evaluer le potentiel protecteur d une hypoxie temporaire profonde contre les rayonne ments de Roentgen produits par un accelerateur lineaire L hypoxie a eté induite par l in jection intraarterielle de microspheres d amidon degradable La dose d irradiation neces saire pour provoquer une certaine reaction dans la patte hypoxique a ete double de la dose donnant la meme reaction sur un groupe temoin Ces resultats indiquent une nouvelle technique pour provoquer une hypoxie locale dans des tissus sains qu il faut proteger dans un champ d irradiation

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HAEMATOLOGIC EVALUATION AFTER RADIATION THERAPY IN HODGKIN S DISEASE

J A VILPO and E M NORDMAN

Recent results of the treatment of malignant lymphoma have been promising n particular using modern irradiation techniques a full and permanent cure seems o be possible and up to 80 per cent of the patients with Hodgkin s disease survive or 5 years (KAPLAN 1972 AISENBERG & QAZI 1976) A total dose of 35 to 45 Gy 3 500–4 500 rad) given during a period of 4 to 7 weeks (KAPLAN & ROSENBERG 1975) has been found necessary to reduce the recurrences as much as possible In advanced cases of Hodgkin s disease multiple cytostatic drug therapy is indicated DEVITA et coll 1970)

After the usual curative doses of irradiation a local depression in the haemato poiesis follows The dose response data for irradiation of human bone marrow are limited SYKES et coll (1964) performed sternal aspirations in patients with localized carcinoma of the breast following 17 to 60 Gy Little or no marrow regeneration was found in 54 of 56 patients given 30 Gy or more up to 84 months after irradia tion RUBIN et coll (1973) used $^{99}Tc^{m}$ S colloid scanning technique for analysing the condition of the bone marrow in 27 patients with Hodgkin s disease at various times before and after intensive irradiation They observed a partial to complete bone marrow regeneration at 40 Gy in 85 per cent of the irradiated sites at two years In 71 consecutive patients irradiated for Hodgkin s disease KUN & JOHNSON (1975) found

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Table 1

Clinical data of 30 patients treated for Hodgkin s disease

Case/Age/Sex	Stage Ann Arbor classification	Grade*	Radiation field	Calculated bone marrow dose (Gy)	Drug therapy	Recurren. at time of marrow biopsy
1/73/M	I A	NS(MC)	Mantle	40	No	No
2/32/F	II A	(NUD)	Mantle	40	Procarb ad 2 5 g	No
3/31/M	III A	NS	Mantle Inv Y	38 22	MOPP ×6 MVPP ×3	No
4/29/M	III B	NS	Mantle Inv Y	42 24	No	No
5/22/F	II B	NS	Mantle	40	No	No
6/31/F	II A	MC	Mantle Inv Y	40 24	CVPP ×12	No
7/23/M	I A	NS	Mantle	40	MOPP ×4 CVPP ×1 ABVD ×1	Yes
8/71/F	III A	NS	Mantle Inv Y	40 24	No	No
9/27/M	II A	NS	Mantle	40	CVPP ×6 COPP ×3 Bleomyc ad 0 3 g	Yes
10/29/F	II A	NS	Mantle	32 4	MOPP ×9 CAVe ×1	No
11/62/F	I B	LP	Mantle	38	No	No
12/20/M	III B	NS	Mantle Inv Y	40 24	CVPP ×6	No
13/35/F	III B	MC	Mantle Inv Y	40 24	CVPP ×6 MOPP ×3 MVPP ×7	Yes
14/50/F	II A	NS	Mantle	48	Procarb ad 4 g	No
15/59/M	II A	(NUD)	Mantle	39	No	No
16/56/M	I A	NS	Mantle	40	No	No
17/65/M	II A	LP	Mantle	40	No	No
18/28/M	III B	(NUD)	Mantle Inv Y	40 24	No	No
19/27/M	II B	LD	Mantle Inv Y	40 14	CVPP ×8 ABVD ×1 MOPP 7	Yes
20 24/M	II A	NS	Mantle	40	MOPP 8	No
21/28/F	III B	LP	Mantle Para a	40 24	MOPP ×1	Yes

Table 1 (*cont*)

Case/Age Sex	Stage Ann Arbor classification	Grade	Radiation field	Calculated bone marrow dose (Gy)	Drug therapy	Recurrence at time of marrow biopsy
22/40/F	II B	NS	Mantle	44	CVPP × 12 MOPP × 15	No
23/65/M	I B	LD	Mantle	30 5	VPP × 4 CVPP × 7	No
24/41/M	II A	LP	Mantle	40	CVPP × 4	No
25/69/F	I A	LP	Mantle	40	No	No
26/59/F	IV	(NUD)	Mantle	40	COPP × 12	No
27/25/M	I B	(NUD)	Mantle	40	No	No
28/70 F	I A	LP	Mantle	40	No	No
29/35/M	III A	LP	Mantle Inv Y	42 25	COPP × 3 CVPP × 6	No
30/31/M	I A	(NUD)	Mantle	40	No	No

See FRANSSILA et coll 1967

no evidence for residual haematologic depression after 5 years of disease free survival even in patients treated initially with total nodal irradiation However the local marrow effects of the irradiation were not recorded Recently KNOSPE et coll (1976) used ^{5}Fe bone marrow scanning from 1 to 73 months after radical irradiation of patients with malignant lymphoma Marrow regeneration was observed in most patients after an interval of 12 months or longer The recovery did not seem to be dose related and the dose of marrow ablation was not defined with doses of 40 to 50 Gy The authors concluded that the erythropoietic function recovered in the irradiated marrow in most patients 1 to 2 years after about 40 Gy

In most cases of effective irradiation the dose reaches the tolerance limit of the bone marrow Thus the exact knowledge of the bone marrow effects of irradiation would be of great importance Furthermore a careful characterization of these effects might bring new light on the understanding of the basic mechanisms of haematopoiesis

The haematologic data obtained 2 to 7 years after irradiation of 30 patients with Hodgkin s disease are now reported with particular emphasis on the local bone marrow effects

Material and Methods

The 30 patients included in the material represent 32 survivors of the total number of 56 consecutive cases irradiated for Hodgkin s disease in this hospital from 1969 to 1973 The megavoltage treatment was delivered with an 8 MeV linear accelerator to mantle fields or with a cobalt equipment according to an individual treatment plan

Lymphography was performed in 27 patients and laparotomy including s[illegible] tomy in 20 patients In 7 patients the disease progressed after the primary treatm[illegible] Two of them have no further signs of disease at the present time and the t[illegible] number of obviously disease free cases was 25 The detailed clinical data of the p[illegible] tients are presented in Table 1

Bone marrow aspirations were performed with a Klima type 1 5 mm (18-g[illegible] needle and 20 ml syringe after local anesthesia Samples were taken both from the sternal manubrium and the posterior iliac spine If the sternal aspiration did not g[illegible] any visible cellular particles the top of the needle was rotated inside the sternum an orbit of 1 to 1½ cm before a new aspiration Both smears and pressing prep[illegible] tions were made for May Grunwald Giemsa (MGG) The amounts of marrow [illegible] reticular tissue (—cellular components of reticuloendothelial system) erythropoiet[illegible] granulopoietic and megakaryopoietic tissue were evaluated semiquantitatively [illegible] coded preparations at microscopy

The haemoglobin concentration white cell count and red cell count were measured with the Coulter Counter S The platelet count was measured from the same EDTA anticoagulated venous sample with the Thrombo counter C Differential coun[illegible] of white cells were made by one experienced laboratory nurse and one of the auth[illegible] examined the red cell morphology from MGG stained films The relative number of peripheral blood reticulocytes was calculated after methylene blue stainin[illegible] randomly chosen patients

Results

The mean blood cell values of the 30 patients are within normal limits (Table [illegible]

In the 5 cases with recurrence the haemoglobin concentration was 106 g/l (male) 131 g/l (female) the white cell count 7 300 × 10^6/l and the platelet count 350 × 10^9/l (mean values) Only one of the recurrence free patients was anemic (Hb 114 g/l) His iron storage was normal Seven cases had thrombocytosis (platelet values me[illegible] 470 range 410–560 × 10^9/l) and 3 slight leukocytosis (10 500 10 700 and 11 [illegible] 10^6/l) All of them were splenectomized

The red cell morphology was characteristic in splenectomized cases with num[illegible] Howell Jolly bodies target cells and irregularly furrowed red cells

All bone marrow samples were rich in blood and marrow fat Iliac bone mar[illegible] aspirations were normal except one (No 20) in which no haemopoietic cells w[illegible] found Instead the appearance of the sternal marrow varied widely A d[illegible] analysis of the haematopoietic cells and marrow reticular cells is presented in Ta[illegible]

Haematopoietic or reticular cells were found in 27 preparations A co[illegible] regeneration of the sternal bone marrow was evident in 5 cases one exposed [illegible] 30 5 Gy and 4 with 40 Gy In addition regeneration of the three haemat[illegible] lineages occurred in one marrow after 40 Gy in 5 to 7 weeks but the cell n[illegible] were low

In many samples the cellular differentiation was abnormal (± in Table 3). In th[illegible]

Table 2

Mean blood cell values

Parameter	Mean ± SD	N	Reference values
Haemoglobin	138 ± 19	17	130–165 (M)
(g/l)	134 ± 9	13	115–150 (F)
Erythrocytes	4 6 ± 0 6	15	4 3–5 6* (M)
(10 /l)	4 4 ± 0 3	12	3 8–5 0 (F)
Reticulocytes*	57 ± 24	9	18–158 **
(10 /l)			
White blood cells	7 200 ± 2 200	30	3 000–10 000*
(10 /l)			
Neutrophils****	4 500 ± 1 700	30	1 830–7 250* *
(10^6/l)			
Monocytes**	390 ± 180	30	200–950 *
(10 /l)			
Lymphocytes ***	2 300 ± 1 100	30	1 500–4 000***
(10^6/l)			
Platelets	340 ± 110	30	150–400*
(10^9/l)			

95 range for healthy adults in this laboratory
* Reticulocytes = erythrocytes × per cent of reticulocytes
* * 95 range for normal adults
* Neutrophils (monocytes lymphocytes) = WBC × per cent of neutrophils (monocytes lymphocytes)

cases the continuance of maturation was defective and many of the haematopoietic cells were morphologically abnormal Nuclear-cytoplasmic desynchronization and poor cytoplasmic maturation were observed Erythropoietic and granulopoietic cells were irregularly bordered and the nuclear cytoplasmic ratio was higher than in their counterparts in normal iliac marrow In granulopoietic series the cytoplasmic maturation was delayed as compared with the stage of the maturation of the nucleus and cytoplasmic basophilia deeper than expected Similarly the haemoglobinization stage was low in erythropoietic precursor cells although the nucleus represented a differentiation stage of a normal polychromatophilic or orthochromatophilic normoblast

In 7 of the 21 reticular cell positive cases no haematophoiesis was seen after 38 to 42 Gy and in additional 9 cases the haematophoiesis was defective as in the cases without reticular cells In two of them abnormal haematopoietic cell were observed

Discussion

The normal blood cell values in the 30 patients indicate that the number and function of haematopeoietic precursor cells is normal but it should be remarked that the distribution of these cells may be quite abnormal

Table 3

Semiquantitative estimates of the haematopoietic precursor cells and reticular cells in the sternal marrow

Case	Sternal dose (Gy)	Interval (years)	Erythro-poiesis	Granulo-poiesis	Megakaryocytes	Reticular cells
1	40	5	−	+	−	++
2	40	7	−	−	−	−
3	38	6	−	±	−	+
4	42	6	±	±	−	−
5	40	3	−	−	−	−
6	40	3	+	+	−	++
7	40	5	++	++	++	++
8	40	5	+	+	+	+
9	40	6	−	−	−	+
10	32 4	7	±	±	−	−
11	38	4	±	±	−	++
12	40	3	−	−	−	++
13	40	6	++	++	++	++
14	48	5	−	−	−	++
15	39	4	−	−	−	++
16	40	5	±	±	−	++
17	40	4	−	−	−	−
18	40	5	±	−	−	++
19	40	5	−	−	−	++
20	40	4	−	−	−	+
21	40	3	−	−	−	++
22	44	3	−	−	−	++
23	30 5	5	++	++	++	++
24	40	5	±	±	−	++
25	40	2	±	−	−	+
26	40	3	++	++	++	++
27	40	3	+	+	−	+
28	40	4	−	−	−	−
29	42	6	−	−	−	−−
30	40	4	++	++	++	++

++ Normal number of cells
+ Decreased number of cells All maturation stages present
± Not all maturation stages present or abnormal morphology
− No (precursor) cells present

Platelet values higher than normal were observed in 7 patients and a slight le[illegible] cytosis in 3 These patients were splenectomized which is likely to be the ca[illegible] the thrombocytosis and of the leukocytosis (McBride et coll 1968 Singer et c 1941) In other recurrence free cases all blood values were within the norm[illegible] per cent range The results are in good agreement with those published by Kn[illegible] Johnson

KNOSPE et coll (1966 1968) have elucidated the basic mechanisms operating after local irradiation of the marrow The late aplasia is correlated with radiation induced loss of sinusoidal structures and the haemopoietic recovery depends upon sinusoidal regeneration In the present material full haemotopoietic regeneration was observed in 5 out of 21 patients given 40 Gy in 5 to 7 weeks Additionally in 7 cases after a dose of 40 Gy some haematopoiesis was observed In 9 sternal aspirations no haematopoiesis was found although these samples are to be considered as representative ones

From the present results it may be concluded that the bone marrow regeneration after irradiation is not an all or none phenomenon The patchy irregular marrow regeneration observed in patients and in experimental animals by KNOSPE et coll (1966 1976) may be analogic to the deficient cell appearance in the bone marrow aspirations of the present patients However another explanation of the existence of morphologically or numerically abnormal haematopoiesis in bone marrow is also possible Animal experiments suggest that the recovery of radiation injured bone marrow may be initiated by stem cells originating from unirradiated bone marrow regions after the stromal regeneration has taken place (CARSTEN & NOONAN 1959 DE VRIES & VOS 1966) In human peripheral blood stem cells usually circulate (CHERVENICK & BOGGS 1971) The seeding of these cells is possible and these haematopoietic precursor cells may be temporarily located in the irradiated marrow Without fully regenerated stroma the marrow does not function in the normal way to maintain morphologically normal haematopoietic colonies or numerically normal haematopoiesis (KABAKOV et coll 1968) The constant injury of the marrow after radical irradiation is apparently caused by the deterioration of the microcirculation and endothelial in nature (RUBIN & CASARETT 1968 ZOLLINGER 1970) The stem cells migrated from unirradiated regions are not able to repair this lesion (KABAKOV et coll 1968 KNOSPE et coll 1966 1968)

KUN & JOHNSON using $^{99}Tc^{m}$ S colloid and KNOSPE et coll (1976) using ^{52}Fe bone marrow scanning noted a higher rate of regenerations in patients following irradiation with 40 Gy than noted in the present material Instead if the abnormal haematopoiesis is not considered a sign of a real marrow regeneration the present results are similar to those published by SYKES et coll (1964) They did not observe sternal marrow regeneration in 96 5 per cent of cases after 30 Gy or more given for mammary carcinoma In the present material the percentage of full regeneration after 38 to 48 Gy was 18 (5/28) No clear correlation between the local marrow regeneration and irradiation of other fields or cytostatic drug therapy was found

A reliable quantitative examination of human bone marrow after irradiation is possible in only a few clinical situations Quantitative evaluation ought to be performed by histologic methods but the trepanation of the sternum and aspiration of marrow samples is difficult Unfortunately neither the nuclide scanning methods nor the direct marrow aspiration biopsy provides a quantitative measure of the cellularity in bone marrow

SUMMARY

Haematologic evaluation of 30 patients 2 to 7 years after radiation therapy for H[illegible] disease was made A complete general recovery of haematopoiesis occurred as [illegible] from the normal or even supranormal blood cell values However in only 5 of 28 p[illegible] was a complete local regeneration of haematopoiesis observed in the sternal marrow [illegible] after 38 to 48 Gy In the other cases haematopoiesis was numerically or morpholog[illegible] abnormal or totally absent

ZUSAMMENFASSUNG

Eine hamatologische Untersuchung von 30 Patienten wurde 2 bis 7 Jahre nach Be[illegible] lung wegen Hodgkinscher Erkrankung vorgenommen Eine vollstandige Regenera[illegible] Hämatopoese wurde erreicht wie aus den normalen und auch supranormalen B[illegible] werten beurteilt werden konnte Jedoch wurde nur bei 5 von 28 Patienten eine k[illegible] lokale Regeneration der Hamatopoese in den Biopsien des Knochenmarks des S[illegible] nach 38 bis 48 Gy beobachtet In den anderen Fallen war die Hamatopoese numerisch [illegible] morphologisch abnormal oder total abwesend

RESUMÉ

Les auteurs ont fait une etude hématologique de 30 malades de 2 à 7 ans après un tra[illegible] ment par les radiations pour une maladie de Hodgkin La numeration des cellules [illegible] qui est normale ou meme supérieure à la normale fait conclure à une restauration co[illegible] et génerale de l hématopoïèse Cependant c est seulement chez 5 malades sur 28 qu [illegible] observe une regéneration locale complète de l hématopoïese sur des biopsies de la [illegible] sternale après une irradiation allant de 38 a 48 Gy Dans les autres cas l hématopoïèse [illegible] numériquement ou morphologiquement anormale ou totalement absente

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FROM THE DEPARTMENT OF RADIATION THERAPY THE BUFFALO GENERAL HOSPITAL
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GENERAL EQUATIONS FOR THE CALCULATIONS OF BIOLOGIC EFFECT RATIOS FOR PARALLEL OPPOSING FIELDS

PEI NAN TSUNG and YEHUDA G LAOR

In considering the iso effect relationship in clinical radiation therapy the use of the NSD concept was proposed by ELLIS (1968 1969) It is based on the fact that the tissue tolerance dose depends on a simplified time dose and fractionation factors with the following relationships

$$D = NSD \times N^{0.24} \times T^{0.11}$$

where D is the total tolerance dose in rad N is the number of fractions given, T is the overall treatment time in days and the constant proportionality is termed NSD (the nominal standard dose in ret) a term which relates to connective tissue tolerance

For a given number of fractions the value of T depends upon the number of fractions per week and can be approximated

$$T = K \times N^{1.13}$$

where K is a constant depending on the number of treatments given weekly (WINSTON et coll 1969)

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By combining eqs (1) and (2) is obtained

$$N = \left(\frac{NSD}{d}\right)^{1\,53} \times K^{0\,13} \quad (3)$$

here $d = D/N$ is the dose per fraction

Once the tolerance of NSD is established the partial tolerance is not the sum of ach individual combined partial NSD but rather defined as

$$PT = NSD \times \frac{m}{N} \quad (4)$$

where N is the number of fractions of the chosen dose which would result in full normal connective tissue tolerance and m is the number of such fractions actually given (ORTON & ELLIS 1973) The partial tolerance can be summed up only by the concept of eq (4) By adapting the concepts of NSD and its partial tolerance two simple systematic formulae in terms of per cent depth doses are derived to compare the biologic effect ratios (BER) of any two points of interest in the treatment volume of two parallel opposing fields treated either one field or both fields at each session

Derivation

The resulting biologic effect ratio at the point of interest for two parallel opposing fields treated alternatively one field per session The following expression is obtained by applying eq (4)

$$\left[\frac{\frac{1}{2}N(t\ n)}{N\left(i\ \frac{n}{2}\right)} + \frac{\frac{1}{2}N(t\ n)}{N\left(i_p\ \right)\frac{n}{2}}\right] NSD(t) \times T_f = PT(i\ ) \quad (5)$$

$$BER(i\ t) = \frac{PT(i\ )}{NSD(t)} = \left[\frac{\frac{1}{2}N(t\ n)}{N\left(i\ \frac{n}{2}\right)} + \frac{\frac{1}{2}N(t\ n)}{N\left(i_p\ \frac{n}{2}\right)}\right] \times T_f \quad (6)$$

where NSD (t) is the maximum tolerance level of normal connective tissue at the tumor bed PT (i) is the sum of the partial tolerance at the location of interested normal tissue other than the tumor bed t represents the location of the connective normal tissue of tumor bed i is the tissue of interest to be compared other than t with the subscripts of a and p of t and i represent the anterior and posterior distances to the surfaces of the skin T_f represents time correction factor N(i n/2) and $N(i_p\ n/2)$ mean total number of fractions at the point of interest with i and i_p respectively when using half fractions of treatments each week This corresponds to doubling of the total treatment time i e all the treatments from one field with n 2 are given first and the other field with n/2 given later This is not the actual case

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In considering the iso effect relationship in clinical radiation therapy the use of the NSD concept was proposed by ELLIS (1968 1969) It is based on the fact that tissue tolerance dose depends on a simplified time dose and fractionation factor by the following relationship (1)

$$D = NSD \times N^{0.24} \times T^{0.11}$$

where D is the total tolerance dose in rad N is the number of fractions given T the overall treatment time in days and the constant proportionality is termed NSD (the nominal standard dose in ret) a term which relates to connective tissue tolerance

For a given number of fractions the value of T depends upon the number of fractions per week and can be approximated (2)

$$T = K \times N^{1.13}$$

where K is a constant depending on the number of treatments given weekly (WINSTON et coll 1969)

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These two generalized equations can be simplified further to find out the biologic effect ratios between the depth of the maximum build up and the connective tissue of tumor site by the fact $P(t_a)=100$ and $t=m$ where m is the depth at maximum build up point

$$BER(m\ t)=\frac{1}{2}\left[\left(\frac{100}{P(t)}\right)^{1\ 573}+\left(\frac{d(t_p)\times P(s)}{d(t)\times P(t_p)}\right)^{1\ 573}\right] \tag{12}$$

and

$$BER(m\ t)=\left[\frac{\dfrac{d(t)\times 100}{d(t_p)\times P(t)}+\dfrac{P(t_p)}{P(t_p)}}{\dfrac{d(t)}{d(t_p)}+1}\right]^{1\ 573} \tag{13}$$

where eqs (12) and (13) are related to single port and double ports of parallel opposing fields treated daily respectively s is the thickness of the patient

A further simplification can be obtained by the following conditions

(1) Assuming that a constant dose at the maximum build up point is given for the two parallel opposing fields at each treatment

$$\frac{d(t)}{P(t)}=\frac{d(t_p)}{P(t_p)}$$

Then eqs (12) and (13) can be rewritten as

$$BER(m\ t)=\frac{1}{2}\left[\left(\frac{100}{P(t)}\right)^{1\ 573}+\left(\frac{P(s)}{P(t)}\right)^{1\ 573}\right]$$

$$=\frac{1400+P(s)^{1\ 573}}{2P(t)^{1\ 5\ 3}} \tag{14}$$

$$BER(m\ t)=\left(\frac{100+P(s)}{P(t)+P(t_p)}\right)^{1\ 5\ 3} \tag{15}$$

(2) Assuming that a constant dose at the tumor site is given for the two parallel opposing fields of each treatment

$$d(t)=d(t_p)$$

eqs (12) and (13) can be rewritten as

$$BER(m\ t)=\frac{1}{2}\left[\left(\frac{100}{P(t)}\right)^{1\ 573}+\left(\frac{P(s)}{P(t_p)}\right)^{1\ 573}\right] \tag{16}$$

$$BER(m\ t)=\left[\frac{100}{2P(t)}+\frac{P(s)}{2P(t_p)}\right]^{1\ 5\ 3} \tag{17}$$

and a time correction factor is needed for eq (5) Concentrating the inter tumor site only by using the relationship of eq (4)

$$\left[\frac{\frac{1}{2}N(t\ n)}{N\left(t\ \frac{n}{2}\right)}+\frac{\frac{1}{2}N(t\ n)}{N\left(t\ \frac{n}{2}\right)}\right]NSD(t)\times T_{cf}=NSD(t)$$

$$T_{cf}=\frac{N\left(t\ \frac{n}{2}\right)}{N(t\ n)}$$

is obtained

The dose d(i) at i_a and i_p with respect to d(t) and depth doses can be expre

$$d(i\ )=\frac{d(t_a)}{P(t\ )}P(i\ )$$

$$d(i_p)=\frac{d(t_p)}{P(t_p)}P(i_p)$$

where P is the percentage depth dose at the respective sites

Substituting eq (7) and (8) into eqs (6)

$$BER(i_a\ t)=\frac{1}{2}\left[\left(\frac{P(i\ )}{P(t_a)}\right)^{1\ 73}+\left(\frac{d(t_p)\ /\ P(i_p)}{d(t_a)\times P(t_p)}\right)^{1\ 535}\right]$$

is obtained

Eq (9) is a general formula which demonstrates the biologic effect ratios of i_a and t for two parallel opposing fields treated alternately through a singl port day

The resulting biologic effect ratio at the point of interest for two parallel o fields treated daily The total dose d (sum) of certain normal tissue interested than the tumor bed which are delivered for each session is

$$d(sum)=d(i\ )+d(i_p)$$

$$=\left[\frac{d(t_a)}{P(t\ )}P(i_a)+\frac{d(t_p)}{P(t\ )}P(i_p)\right]$$

and by using eq (4)

$$BER(i_a\ t)=\left[\frac{\frac{d(t_a)}{P(t_a)}P(i_a)+\frac{d(t_p)}{P(t_p)}P(i_p)}{d(t\ )+d(t_p)}\right]^{1.5\ 3}$$

is obtained

Eq (11) is the general formula of the biologic effect ratio of points i_a for two parallel opposing fields treated daily Both eqs (9) and (11) are based same number of fractions per week

Table 3

Maximum tolerance dose (1900 ret) to the skin for two parallel opposing fields

		Constant skin dose		Constant tumor dose	
		Anterior	Posterior	Anterior	Posterior
ingle port per day	Tumor dose (ret)	1 466	1 130	1 423	1 157
	Skin dose (ret)	1 900	1 900	1 900	1 900
Double port per day	Tumor dose (ret)	1 509	1 509	1 618	1 384
	Skin dose (ret)	1 900	1 900	1 900	1 900

able 1 The biologic effect ratio is always greater than one in this example The goal of 1 900 ret to the tumor bed is hardly reached without exceeding radiation tolerance of the skin (Table 2) If the maximum tolerance level is 1 900 ret to the skin the dose to the tumor bed will be reduced accordingly from Table 3 The higher the tumor dose in ret the greater the chance for curing So within the same conditions treating double ports per day is always superior to single port treatments per day for both constant skin dose and constant tumor dose

The choice between using the constant skin dose or the constant tumor dose for parallel opposing fields is based on the clinical preference

Discussion

It is well known that the highest dose level for two parallel opposing fields is mostly located at the depth of the maximum build up and the tolerance level of normal tissue at the surface will be reached prior to the connective tissue of the tumor site The results of treating double fields per session favorable to single field per session are not new The purpose of this report is to give some systematic analysis from the biologic point of view Eqs (9) and (11) are generalized equations to compare any two locations within the treatment volume for two parallel opposing fields treated single session daily or double sessions daily Typical examples of the biologic effect ratio are given for comparing the depth of the maximum build up and connective tissue of the tumor site as shown in eqs (14–17) All of the above derivations and arguments are based on the NSD concept and its partial tolerance concept A real numerical ratio can be obtained by using the above equations which give a better understanding to realize the dosage distribution at different treatment plans and locations

SUMMARY

The tolerance level of normal tissue which is the concept of NSD is the limiting factor in radiation therapy It is well known that the two parallel opposing fields should be treated at

each session instead of alternating one field per session The biologic effect ratios [illegible] the normal tissue at the depth of maximum build up and the midline for parallel [illegible] fields were published by ELLIS et coll General formulae are now presented [illegible] biologic effect ratio at any two locations in terms of per cent depth doses in the [illegible] volume for parallel opposing fields Examples at the depth of maximum build-up and [illegible] depth of the connective tissue at the tumor site are also given

ZUSAMMENFASSUNG

Das Toleranzniveau des normalen Gewebes welches das Konzept der NSD ist [illegible] den begrenzenden Faktor bei der Strahlentherapie Es ist wohl bekannt dass die [illegible] parallelen gegenuberliegenden Felder bei jeder Behandlung behandelt werden soll [illegible] stelle umwechselnd ein Feld per Behandlung Die biologischen Effekt Verhältniswerte [illegible] schen den Normalgeweben zu der Tiefe des maximalen Build up und der Mittelli [illegible] parallele gegensatzliche Felder sind von ELLIS et coll publiziert worden Generelle For[illegible] werden nun gegeben um biologische Effekt Verhaltnisse an jeder von zwei Lokalis[illegible] in Begriffen von Prozent Tiefendosen im behandelten Volumen von parallelen ge[illegible] lichen Feldern zu erhalten Beispiele fur die Tiefe des maximalen Build up und [illegible] wissen Tiefe fur das Bindegewebe am Platze des Tumors werden gegeben

RÉSUMÉ

Le niveau de tolerance du tissu normal qui est le concept de la NSD est le facteur [illegible] dans le traitement par les radiations Il est bien connu que deux champs parallèles [illegible] devraient etre traités à chaque séance au lieu d alterner un champ par séance Les [illegible] ports d effet biologique entre le tissu normal à la *profondeur* d accumulation max[illegible] et sur la ligne médiane pour des champs parallèles opposés ont été publiés [illegible] et collaborateurs Les auteurs présentent maintenant des formules génerales [illegible] rapport biologique pour deux localisations quelconques en terme de pourcentage de [illegible] en profondeur dans le volume de traitement pour les champs parallèles opposés Is [illegible] aussi des exemples à la profondeur d accumulation maximale et à une certaine prof[illegible] du tissu conjonctif au siège de la tumeur

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DOSIMETRY INTERCOMPARISONS FOR EVALUATION OF LATE EFFECTS OF IONIZING RADIATION

J J BROERSE J ZOETELIEF and K J PUITE

Evaluation of the late somatic effects of ionizing radiation in mammalian organ ms is of great importance for assessment of the risks of low level radiation ex osure Since this type of research requires large scale experiments and long term ommitments of personnel and facilities a joint project was initiated by a group of istitutes cooperating within the European Late Effects Project Group (EULEP) A prerequisite for coordination of research programs is the standardization of xperimental methods and materials such as exposure arrangements and dosimetry athology and the quality of experimental animals

Investigations in radiation biology and radiation therapy have demonstrated that differences of 10 per cent in absorbed dose will produce clearly observable variations in biologic response In general cell survival analyses do not allow the prediction of variations in absorbed dose determinations smaller than 5 per cent It has been sug gested therefore that an accuracy of 5 to 6 per cent and a precision of 2 to 3 per cent is required for the determination of absorbed do e in biologic applications (BROERSE & MIJNHEER 1976) It must be recognized that these requirements are more severe than generally encountered in radiation protection Taking into account the estimated precision and uncertainty of the TLD system (1 2 per cent and 3 per cent re pec tively) the following recommendations were formulated (cf BROERSE & PUITE 19 3)

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(1) The accuracy of the dosimetry is considered to be satisfactory when the mean value of the results from a laboratory differs by less than 5 per cent from the standard value When a difference between 5 and 10 per cent from the standard value exists a small discrepancy in the dosimetry is indicated If the difference is more than 10 per cent a recalibration of the roentgen ray dosimetry system is recommended

(2) A standard deviation in the relative absorbed dose values below 3 per cent indicates a correct precision When the standard deviation is between 3 and 5 per cent some doubts arise about the precision If the standard deviation is more than 5 per cent, attention must be paid to the reproducibility of the irradiations

The first EULEP dosimetry intercomparison project performed in 1970 and 1971 (PUITE et coll 1972) indicated several discrepancies concerning the absolute dosimetry and the exposure conditions employed at the participating institutes The results of this project were evaluated and a protocol for EULEP dosimetry, including a code of practice was prepared (EULEP 1972) The second series of intercomparisons of absorbed dose and dose distribution was carried out in 1973 (BROERSE and PUITE) it was performed to check on the improvements made after the first intercomparison In this project special emphasis was placed on irradiation of the mouse phantoms in the cages actually in use for the mouse irradiations at the participating institutes In the three consecutive sessions of the third dosimetry intercomparison from September 1976 to February 1977 16 groups from eight countries participated (the sequence is different from that in the tables and figures presenting the results)

1 P Tambourin Unite de Physiologie Cellulaire de l INSERM Orsay France
2. E H Betz, Institut de Pathologie Liege Belgium (Did not participate in the third intercomparison)
3 P van Caneghem Laboratory of Radiobiochemistry of the University of Leuven Belgium
4 J A G Davids E C N Petten The Netherlands (Did not participate in the third intercomparison)
5 K J Puite Association EURATOM ITAL Wageningen The Netherlands
6 J H Mellink Radiotherapy Department of the University Hospital, Leiden The Netherlands
7 O Balk Strahlenbiologisches Institut der Universitat Munchen und Institut fur Biologie der G S F Neuherberg Germany
8 A M Dancewicz, Institute of Nuclear Research Department of Radiobiology and Health Protection Warszawa Poland
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10 G Mattelin Radiobiology Department, CEN/SCK Mol Belgium
11 E. B Harriss Abteilung fur Klinische Physiologie der Universitat Ulm Germany
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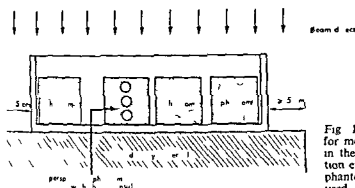


Fig 1 Exposure arrangement for mouse phantoms employed in the dose and dose distribution experiments with adjacent phantoms in the cage actually used for mouse irradiations

3 B Hogeweg Radiobiological Institute TNO Rijswijk The Netherlands
4 A L Batchelor Medical Research Council Radiobiology Unit Harwell England
5 A Dixon Brown Radiobiology Laboratory Churchill Hospital Oxford England
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8 G Scarpa Division of Radiation Protection CNEN CSN Casaccia Roma Italy

This third intercomparison was considered to be essential for a periodical check on the dosimetry procedures and for the benefit of the new groups joining EULEP in the intervening years In accordance with previous procedures the intercomparison was performed by using mailed thermoluminescent (TL) dosemeters

In this communication the results of the third intercomparison are discussed with reference to those of the previous measurement series Some improvements have been made however for some participants the variations in absolute dosimetry and in dose distribution over the mouse phantom are still considered to be unsatisfactory The need for repeated dosimetry intercomparisons seems to be indicated

Materials and Methods

All participants received an acrylic plastic mouse phantom containing 3 LiF filled test capsules together with an irradiated control capsule for each session The phantom was to be placed in the central part of the mouse cage used for routine animal exposures in accordance with the arrangement illustrated in Fig 1 Additional phantoms equal to the number of mice irradiated simultaneously or an equivalent amount of side scattering material were to surround the test phantom The

Table 1

Correction factors for energy dependence of the thermoluminescence signal of lith·um f·ex

Radiation quality of the incidence beam			Sensitivity of LiF (TL reading per unit absorbed dose) in muscle tissue rela·t· that for ⁶⁰Co gamma rays	
HVL (mm Cu)	Effective energy (keV)*	Equivalent HVL in phantom (mm Cu)	Free in air	In mouse phantom with full scatter conditions
0 5	62	0 40±0 06	1 27	—
0 6	66	0 45±0 06	—	—
0 9	78	0 63±0 06	1 197	1 277±1
1 0	82	0 68±0 06	1 184	1.263±1
1 1	85	0 74±0 06	1 177	1 256±1
1 2	88	0 78±0 06	1 170	1 249±1
1 3	92	0 84±0 06	1 164	1.24?±1
1 45	96	0 93±0 06	1 156	1 233±1
1 5	98	0 95±0 06	1 152	1.230±1
1 7	104	1 05±0 06	1 145	1 223±1
2 0	112	1 21±0 06	1 136	1.213±1
2 1	115	1 26±0 06	1 136	1 213±1
2 2	117	1 33±0 06	1 135	1 208±1
3 0	137	1 75±0 06	1 134	1 155±1
3 6	154	2 10±0 06	1 134	1 143±1
¹³⁷Cs	662	—	1 034	1 034±2
⁶⁰Co	1 250	—	1 000	1 000±2

* Brit J Radiol (1972) Suppl No 11

participants were asked to perform the irradiations in such a way that th· test ca· at the central position of the mouse phantom would receive an absorbed dose of ?C in soft tissue and the irradiation could be considered as uniform (a ratio of less th· 1 15 between maximum and minimum absorbed dose according to the ICR· (1963) recommendations) An HVL of at least 1 5 mm Cu was recommen·d. T· irradiated control capsules were added to investigate possible influences of p·· transport

The procedure for handling the thermoluminescent material was ess· ·· ·· the same as during the former intercomparisons A mean TL value was obta··· ·· 7 readings from one capsule and the sensitivity of the TL reader was checked · the aid of a ¹⁴C light source A fading correction of 0 03 per cent per day af·· · posure was applied Correction factors for the energy dependence of LiF ·· introduced (Table 1) on the basis of the HVL values stated by the p·· (PUITE & CREBOLDER 1974) The HVL values quoted by the participants ··· pared with the expected HVL value based on the combination of the e··· ·

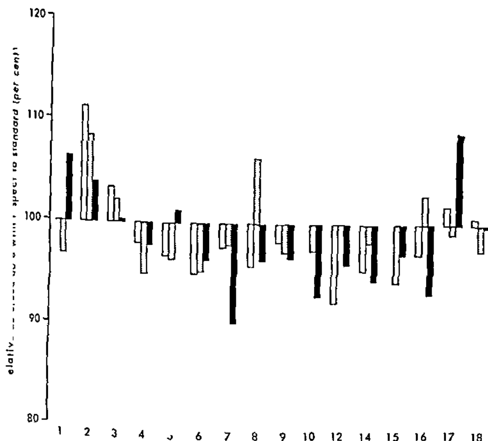


Fig 2 Results for absorbed dose in the central capsule of the mouse phantom relative to the dose obtained from the standards laboratory for the participants in the three consecutive sessions of the third EULEP dosimetry intercomparison project ▭ first ▨ second ■ third session

voltage and filtration Standardization of the roentgen dose was obtained from exposures of capsules free in air at the standardization laboratory of the National Institute for Public Health Bilthoven The Netherlands

The estimated uncertainty in absorbed dose derived by the TLD system is about 3 per cent resulting from 0 4 per cent in the reproducibility of the reading of the LiF capsule 0 3 per cent in the reproducibility of the light output from the ^{14}C source and uncertainties of 0 5 per cent in the fading correction 1 per cent in the correction for energy dependence (2 per cent for ^{60}Co gamma rays) and 1 per cent in the exposure delivered by the standards laboratory The estimated precision of the TLD system for the different sessions for each participant was about 1 2 per cent obtained by taking the square root quadratic sum of the uncertainties mentioned excluding that for energy dependence

The spread in effective energy for different positions in the mouse phantom is

Table 2

Mean relative absorbed dose and corresponding standard deviation for 1971 1973 and 19 6 [illegible] dosimetry intercomparisons

Participants	1971 intercomparison		1973 intercomparison		1976 intercomparison	
	Mean	Stand dev (per cent)	Mean	Stand dev (per cent)	Mean	Stand dev (per cent)
1	1 169	1 5	0 929	1 8	1 011	1 6
2	1 045	0 7	1 027	2 7	1 079	3 5
3	1 049	1 9	1 078	4 5	1 019	1 6
4	1 017	1 5	0 985	0 9	0 969	1 7
5	0 996	2 1	1 019	2 3	0 982	[illegible]7
6	0 953	2 0	0 959	5 9	0 956	0 7
7	0 830	13 3	0 850	6 7	0 95[illegible]	4 5
8	1 125	5 9	0 992	3 4	0 995	6 0
9	1 010	0 4	1 011	0 9	0 974	0 7
10	1 090	2 5	1 028	7 2	0 951	3 5
11	0 977	0 6	0 968	2.0	—	—
12	—	—	1 070	0 7	0 960	4 1
13	—	—	0 979	0 1	—	—
14	—	—	1 013	1 3	0 960	2.1
15	—	—	—	—	0 9[illegible]6	1 9
16	1 041	0 3	—	—	0 976	5 0
17	1 123	11 2	—	—	1 033	5 0
18	—	—	—	—	0 993	1 6

small The dose distribution may therefore be derived directly from the TL [illegible] of the LiF dosemeters at the entrance central and exit position in the [illegible] When a difference in TL reading of entrance and exit capsule relative to [illegible] reading of the central capsule was found to be below 14 per cent the dose [illegible] tion over the mouse phantom was considered to be acceptable according to IC[illegible] (1963) recommendations

Results and Discussion

The LiF data from the sixteen participating institutes have been compared [illegible] those obtained from the standards laboratory The results obtained for the [illegible] absorbed dose (derived from the readings of the central capsules) of the [illegible] secutive sessions of the third EULEP dosimetry intercomparison are given in F[illegible]

With respect to the accuracy of the relative absorbed dose for the particip[illegible] the third intercomparison it can be concluded that the values of 15 out of 16 [illegible] are satisfactory and that a small discrepancy is indicated for only one insti[illegible] precision of the dosimetry of 9 out of 16 participants was found to be corr[illegible] 6 out of 16 institutes the results gave reason for doubts and one participant [illegible]

Table 3

Evaluation of results of the 1971 1973 and 1976 EULEP dosimetry intercomparisons

	Difference from standard dose		
	$\Delta D \leq 5$	$5 < \Delta D \leq 10$	$\Delta D > 10$
1971	8/13	0/13	5/13
1973	10/14	3/14	1/14
1976	15/16	1/16	0/16
	Standard deviation of absorbed dose values		
	$\sigma_D \leq 3$	$3 < \sigma_D \leq 5$	$\sigma_D > 5$
1971	10/13	0/13	3/13
1973	9/14	2/14	3/14
1976	9/16	6/16	1/16

	Absorbed dose distribution			
	$D_{max}/D_{min} < 1.06$	< 1.10	< 1.15	> 1.15
1971	1/12	2/12	5/12	7/12
1973	1/13	5/13	10/13	3/13
1976	2/15	5/15	11/15	4/15

pay attention to the reproducibility The dose distributions of 11 out of 15 participants could be considered as uniform

As can be seen from Table 2 for one participant (number 2) a difference of 8 per cent from the standard dose value and a moderate precision (±3 5 per cent) were observed whereas for another participant (number 8) a poor precision (±6 per cent) was demonstrated Both participants discovered a source for their errors namely a faulty ionization chamber (participant number 2) and an unreliable electrometer (participant number 8) An additional small scale intercomparison showed that the discrepancies had disappeared

The results obtained for the mean relative absorbed dose of the 1971 1973 and 1976 EULEP dosimetry intercomparisons appear in Table 2 The dose distributions obtained for the different participants in the three intercomparisons are summarized in Fig 3 For the radiation qualities employed for the routine mouse irradiation considerable variations of the dose are observed over a depth of 2 cm in the phantom

An evaluation of the results of the three EULEP dosimetry intercomparisons is presented in Table 3 Considerable progress has been achieved with respect to the differences from the standard dose In the last intercomparison 15 out of 16 participants were able to perform their dosimetry with an accuracy better than 5 per cent These improvements can be partially attributed to site visits by members of the EULEP dosimetry committee to some institutes showing appreciable discrepancies

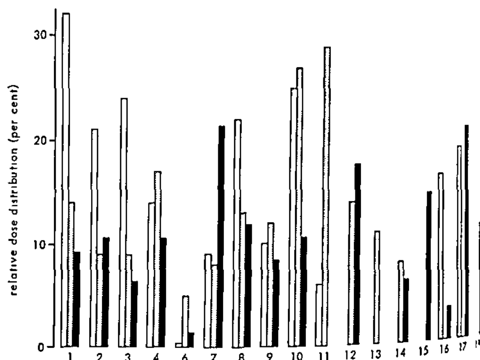


Fig 3 Results for dose distribution over the mouse phantom for the participants in the 19[illegible] and 1976 EULEP dosimetry intercomparison projects respectively The dose distribution is de[illegible] as the difference of TL reading of entrance and exit capsule relative to the TL reading of the ce[illegible] capsule ($TL_{entrance} - TL_{exit}/TL_{central}$) ▭ first ▨ second ■ third intercomparison

Where the standard deviations of the absorbed dose values of the individual pa[illegible] pants are concerned the improvements are only marginal extremely large sta[illegible] deviations are no longer observed in the last intercomparison series It can fir[illegible] be concluded from Table 3 that between the first and the second intercompa[illegible] sessions considerable improvements have been made with regard to the homoge[illegible] of the dose distribution whereas the results of the second and third intercompa[illegible] are comparable The need for improvement of the dose distribution is still ind[illegible] for 4 out of 15 institutes

It should be realized that for investigations in radiation biology under cond[illegible] of uniform irradiation the inevitable variations in absorbed dose through[illegible] volume of interest should not be large enough to significantly affect the b[illegible] response considered The criterion for uniform irradiation has previously be[illegible] formulated by the ICRU (1963) as a ratio of less than 1 15 between maxim[illegible] minimum absorbed dose Differences of 10 per cent in absorbed dose are e[illegible] the biologic endpoint From Table 3 it can be concluded that 10 out of 15 part[illegible] in the EULEP program will have to modify their exposure arrangements in ord[illegible] to comply with a maximum ratio of 1 10 as a new criterion for uniform irra[illegible] In accordance with the recommendation for accuracy of absorbed dose de[illegible]

ons a maximum ratio of 1 06 could be considered This would imply that only 2 ut of 15 participants satisfied this demand during the last EULEP dosimetry inter omparison

Conclusions

The results of the last EULEP roentgen ray dosimetry intercomparison project re satisfying with regard to the assessment of the absorbed dose As far as the preci on of the absorbed dose values are concerned the improvements are only marginal discrepancies observed in the results of two participants could be solved by an addi onal small scale intercomparison With respect to the dose distribution over a nouse phantom a number of participants will have to make improvements

The intercomparison projects provided the participants with the opportunity of hecking the accuracy and precision of their irradiations and the homogeneity of he dose distributions It has to be realized that in several countries for instance Belgium and Italy the possibilities for calibration at a standards laboratory are not vailable Repeated intercomparisons provide information on the long term ap- propriateness of irradiation procedures and stimulate the participants to improve heir dosimetry Special assistance to institutes showing discrepancies have resulted n improvements on a number of occasions The intercomparisons are certainly aluable for new participants and for groups which have installed new irradiation arrangements The intercomparison measurements revealed unexpected discrepancies dosimetry procedures at different institutes and this led to the requirement of repeated dosimetry intercomparisons at intervals of 2 to 3 years It can be concluded hat the stated limits for accuracy (5 per cent) and precision (3 per cent) are adequate o discover inconsistencies in dosimetry The recommendations for the homogeneity of the irradiations might have to be reconsidered in the near future

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SUMMARY

In 1971 1973 and 1976 intercomparisons of absorbed dose and dose distribution over a mouse phantom for roentgen irradiation were performed as part of the program of the European Late Effects Project Group (EULEP) Sixteen institutes from 8 countries partici pated in the sessions of the third intercomparison In general progress has been made concerning accuracy and precision of the dosimetry in 2 cases discrepancies could be

resolved after additional measurements With regard to the dose distribution over a mouse phantom the results are not satisfactory 4 out of 15 participants are still unable to perform uniform irradiations The necessity of repeated intercomparisons is clearly demonstrated to allow a comparison of biologic results obtained in cooperative research programs

ZUSAMMENFASSUNG

In den Jahren 1971 1973 und 1976 wurden gegenseitige Vergleiche uber absorbierte Dosis und Dosis Verteilung fur Rontgenstrahlen durch ein Mausephantom als Teil eines Programmes der europaischen Spateffekt Projektgruppe (EULEP) durchgefuhrt Sechzehn Institute aus 8 Landern nahmen an den Sitzungen des dritten gegenseitigen Vergleiches teil Fortschritte konnten bei der Genauigkeit und Prazision der Rontgenstrahlen Dosimetrie gemacht werden In 2 Fallen konnten nach zusatzlichen Messungen Unterschiede geklärt werden In bezug auf die Dosis Verteiling durch ein Mäusephantom waren die Ergebnisse nicht befriedigend 4 von 15 Teilnehmern sind noch nicht in der Lage eine gleichmäßige Bestrahlung durchzufuhren Die Notwendigkeit fur wiederholte gegenseitige Vergleiche wurde deutlich um einen Vergleich biologischer Ergebnisse aus kooperativen Forschungsprogrammen zuzulassen

RÉSUMÉ

En 1971 1973 et 1976 on a effectué des comparaisons mutuelles des doses absorbées et des distributions de la dose en travers d un phantome de souris pour les irradiations par rayons de Roentgen etant une partie du programme coopératif de recherches en Europe sur les effets tardifs du rayonnement (EULEP) Seize instituts de 8 pays ont pris part aux séances de la troisième comparaison mutuelle *En general on a fait des progrès concernant l exactitude* et la precision de la dosimétrie des rayons de Roentgen Dans deux cas on a résolu des divergences apres des mesures supplémentaires En ce qui concerne la distribution de la dose en travers d un phantome de souris les resultats ne sont pas satisfaisants Quatre des quinze participants ne peuvent pas encore réaliser des irradiations uniformes La nécessité des comparaisons mutuelles repétées est indispensable pour une comparaison des résultats biologiques obtenus des programmes de recherches coopératifs

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IMAGE INTENSIFIER TOMOFLUOROGRAPHY

Experimental evaluation and clinical potentialities

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A tomographic exposure is usually recorded directly on roentgen film However ven in the early phase of development the idea of tomofluoroscopy was presented y POHL (1930) one of the pioneers of tomography The first practical realization of omofluoroscopy—la stratiscopie—was described by PONTHUS & MALVOISIN (1937) ising a moving double mirror system behind the fluorescent screen Later JANKER 1942) and LYSHOLM (1944) reported on their methods of tomofluorography i e n indirect method of making tomograms by photographing the image on the creen The Odelca type of photofluorographic recording of a tomographic image n clinical situations was analyzed by BERG (1953) and GEBAUER (1953 1954) nteresting results with a similar technique used with transverse axial tomography ave also been achieved in localizing mass lesions for therapeutic purposes (BADER & SCHIER 1955 HOLSTI & EISTOLA 1965)

However these methods have two drawbacks making them unsuitable for general se the radiation dose is 2 to 4 times higher and the resolution capacity much ower (MTF about 1 per/mm) than in conventional tomography

In recent years the applicability of roentgen television to tomography has been nvestigated (DUMMLING 1969 FRIMANN DAHL & KÜHL 1970 CHRYSLER 1970 ASSER et coll 1971 REICHMANN 1972) The two main aspects under consideration

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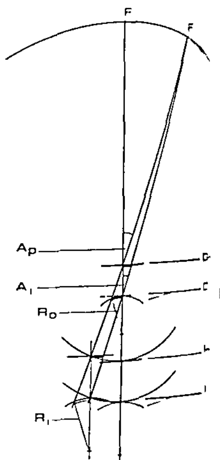


Fig 1 The basic geometry of the image intensifier (I I) tomography F = the focus O_p = the primary object plane I_p = the primary image plane O_i = the object plane of I I tomography I_i = the image plane of I I tomography (input phosphor) A_p = the primary tomographic angle A_i = the angle of I I tomography in the same tube position ($A_p > A_i$) R_o = the radius of cut section in I I tomography R_i = the radius of input phosphor surface The values of FO_p and FI_p in primary tomography are known The unknown values of FO_i FI_i R_o and R_i ought to be determined in I I tomography Particularly the recognition of the precise value of O_pO_i is important for object resetting

have been (1) plane determination by means of tomofluoroscopy and (2) the con[illegible] vertibility of the video signal into a perceptible tomogram The difficulties [illegible] by the latter due to the intrinsic properties of the video technique itself will not [illegible] solved easily Undoubtedly the idea of true videotomofluoroscopy is very [illegible] tive but at present other means of a pseudo character must be [illegible] registering tomograms with a TV chain

Image recording in TV tomofluoroscopy

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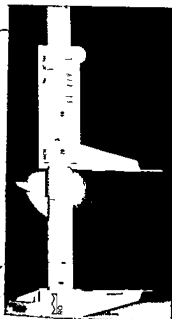


Fig 2 A sliding gauge tomometer with 2 metal wires of 0 2 mm thickness as the plane indicators At the distance of 64 mm each of the wires was depicted sharp (Fig 3) indicating the precise value of O_pO_t

register the entire tomographic space image with a single sweep The idea of this space image was realized previously (ZIEDSES DES PLANTES 1932 WATSON 1939 1951 VIETEN 1940 MARSTRANDER 1954) and the usual simultaneous multisection tomography is based on this principle A peculiar method inherent in the concept of tomography is Serieskopie introduced by ZIEDSES DES PLANTES (1938) The technique has undergone a renaissance in its original form i e in films (MILLER et coll 1971) with modifications resulting in tomosynthesis (GRANT 1972) or on a purely electronic level (BAILY et coll 1973 1974) A possible subject for discussion is whether seriescopy is a true tomographic technique or something else giving the same result In any case this technique makes it possible to produce videotomograms but it is very expensive The methods of DÜMMLING and BAILY et coll are complicated and—at present—on a purely laboratory scale Their advantages are the minute radiation dose and the reproducibility of a tomographic image at any section level Their main disadvantage is the low resolution capacity compared with conventional tomography

Direct image intensifier tomofluorography Fluorography using 70 or 100 mm films is an established proc dure in most roentgen departments However only KAUDE et coll (1973 1974) have reported the possibility of using the same method in tomography employing 70 mm film and yielding a satisfactory image quality They pointed out that improvement in quality is achieved by using a caesium iodide intensifier tube It must be supposed that spot film tomofluorography will have many advantages over the conventional technique on the one hand and over the

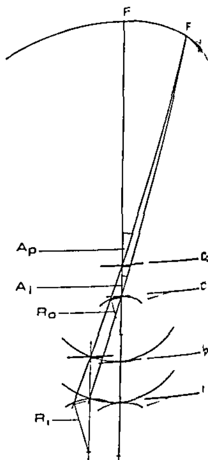


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Table 1

Magnification factors at image levels I_p and I_i

Magnification	Plane I_p	Plane I_i		
	Full size film	100-mm film	TV screen 30 cm	TV screen 33 cm
Geometric (M_g)	1 4	1 4	1 4	1 4
Electron-optic (M_e)	—	0 57	1 10	1.25
Total $M_t = M_g$ M	1 4	0 8	1 55	1 75

he tomographic movement was linear according to the Grossmann principle The ptional angles and corresponding exposure times were 10 -0 8 s 16 -1 3 s and 1 -3 2 s The mechanical movement was an arc of 40 and the tomographic expo- ure occurred symmetrically in relation to the neutral position The cassette carrier as adjustable in the direction of the central beam The maximum FFD was 112 cm ne FOD then being 80 cm The focus size used was 0 6 mm The image intensifier as a Sirecon RPV 17 H (Siemens Erlangen) a caesium iodide tube with resolution ower at the image center of about 4 4 P/mm The image intensifier was arranged nder the cassette carrier and they both performed a parallel movement during omography The diameter of the input aperture was 170 mm The spot film camera sed was a Sircam 100 (Siemens Erlangen) with a film size of 100 × 100 mm

In conventional tomography Kodak XG 14 films in Kodak X omatic cassettes vith regular intensifying screens and in tomofluorography Cronex SF 2 films manufactured by Dupont were used The exposure times in tomofluorography were the same as in the conventional technique

Preliminary arrangements and measurements Before the proper disposal of the 100-mm technique the following rearrangements and measurements were performed

(1) The exposure control unit was readjusted to make the 100-mm camera operate luring tomographic exposure

(2) The unknown geometric extents (Fig 1) were measured These were the unknown distances between object planes (O_pO_i) and image planes (I_pI_i) A sliding gauge tomometer (Fig 2) was placed on the object level perpendicular to the recording planes To facilitate centering the exact object a thin lead marker 1 mm² n size was inserted at the center point of the glass cover of the input aperture Thus the marker lay slightly above the real surface of the input phosphor Fig 3 hows the initial position of the measure elements and the control tomograms of both object planes at a distance of 64 mm ($= O_pO_i$) It is not possible to measure the distance I_pI_i directly but because the geometric magnification is the same in both tomographies i e 1 4 the value of I_pI_i will be 90 mm

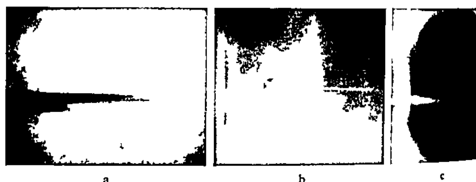


Fig 3 a) A videofluorogram of tomometer indicator wires and the input lead marker superimposed in neutral tube position b) Tomogram and c) 100-mm tomofluorogram depicting the wires as indicated in Fig 2 Also the line drawn by the lead marker in (c) is indicative of the small [illegible] between it and the proper input phosphor surface

complex electronic methods on the other It may be said to be a compromise between a proven method and ultra modern ideas The most important advantage of this technique might be in its close correlation to TV tomofluoroscopy the correct plane determined fluoroscopically is immediately recordable in the film without resetting the position of the object plane to the corresponding image plane as in previous techniques (CHRYSLER 1973) The small film camera could also be used as a [illegible] tool of tomometry the right plane can easily be probed with the spot tomograms before the final recording on ordinary film

The nature of the tomofluorographic image must be analyzed in detail before it can be settled to what extent tomofluorography with 70-mm and 100-mm film can be used as a diagnostic method per se in clinical practice and which are the most suitable subjects In previous works on TV tomofluoroscopy one innate obstacle was noted the spherical form of the input phosphor of the image intensifier A [illegible] tion has been drawn to the constructions with a plane input phosphor which solves this problem (LASSER et coll 1971 REICHMANN 1972) It seems unlikely that these will be available in clinical departments for quite some time and the old tube types must still be used Thus it seems reasonable to clarify the innate characteristics of the tomographic image passing through such a tube and recorded at its output [illegible] with the spot film technique or with a TV camera

Present investigation

The intention was (1) to demonstrate the general problems encountered in image intensifier tomography with special attention to the peculiar geometry of the section and (2) to compare the image quality of 100-mm tomofluorography [illegible] conventional tomography

Radiographic equipment and material The experiments were carried out [illegible] Mimer III stand (Siemens Elema Stockholm) originally designed for neuroradiology

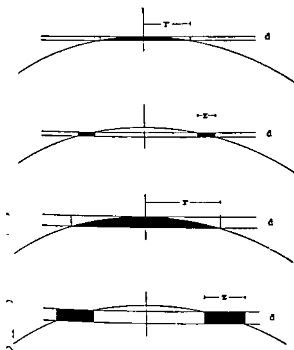


Fig 5 Schematic illustration of the situations described in Fig 4 A difference of section thickness (d and d) causes the different dimensions of the sharp image on the input phosphor The part of the plane like sharp space image is illustrated as black From d >d follows r >r and z >z (cf Fig 6)

ie meter had to be left a correction coefficient of 0 98 was taken into consideration t that level The object diameters were measured to 100 mm The results are given 1 Table 1

Tomographic image on input phosphor

A detailed analysis of the factors influencing tomofluorographic image quality icludes a multiplicity of factors of the tomographic technique itself and those icluded in the electron optic image transfer In addition to the stationary elements iere may also be temporary elements causing disturbances in the sensitive electronic ystems Assuming that the basic difference between the conventional tomograph nd the tomofluorograph i caused by the geometry of the input phosphor the ther parameters can be disregarded The tomographic section is usually considered s a plane This is the case when ordinary roentgen film is used In fact the section ill always take the form of the recording surface Only the dimensions will vary in roportion to the geometric magnification WATSON (1951) demonstrated this in rawings and films where tomograms were obtained of curved and even of spiral lanes VIETEN (1956) discussed the same problem of a photofluorographic nature n tomography

To obtain a preliminary impression from the form of the section as it appears n the 100 mm film a metal mesh (36 meshes per cm² wire thickness 0 3 mm) ompressed between two plexiglass plates 50 mm thick and placed horizontally was

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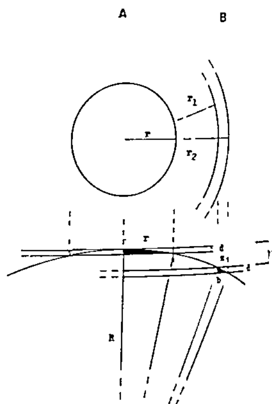
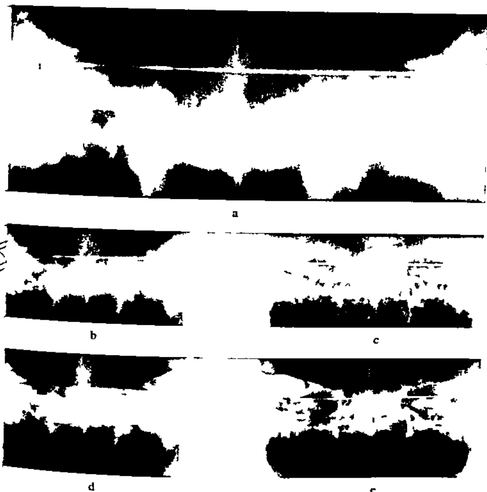


Fig 6 A plane geometric inspection of the situations where a plane of definite thickness (d) is tangential to (A) or intersects (B) a spherical surface of known radius (R) It is analogous to descriptions in Figs 4 and 5 R represents the radius of the curved input phosphor r = the radius of the sharp image area r_1 = the distance of the inner margin and r_2 = the distance of the outer margin of the sharp image zone from the perpendicular central axis (= R) u = the height difference between plane positions The following equations will be obtained (A) $r = \sqrt{2R\,d - d^2} \approx \sqrt{2R\,d}$ The latter case will be more complicated (B) $z = r_2 - r_1 = \sqrt{2R\,(u+d) - (u+d)^2} - \sqrt{2R\,u - u^2}$

tomographed in succession with small intervals in height In the conver[illegible] tomogram the mesh image was sharp at all points when the mesh was a[illegible] object level (O_p) and the blurring was homogeneous out of this plane When the mesh was moved at the object level of the input phosphor (O_i) i e 64 mm be[illegible] the previous plane the mesh image was sharp only on a small central circular area of the 100-mm film (Fig 4 a b) In tomofluorograms taken further under th[illegible] series of concentrical rings of sharp mesh images were obtained (Fig 4 c d) The width of the sharp central areas and that of the sharp circular zones depend[illegible] tomographic angle used This phenomenon is described in the schematic dra[illegible] of the plane geometry illustrated in Fig 5 This is a simplification of the [illegible] when the space image of the mesh is considered as a concrete plane of a [illegible] thickness In this instance the approximate section thickness was evaluated [illegible] the height range where no blurring of the mesh image could be observed [illegible] systems these were about the same 1 mm with an exposure angle of 31 a [illegible] with an angle of 10 The corresponding angles in tomofluorography are [illegible] smaller ($A_p > A_i$) but this was disregarded

As MATTSSON (1972) remarked the concept of cut thickness in tom[illegible] ought to be used with caution because only the defectiveness of th[illegible] systems will give the third dimension the thickness to a purely mathematical [illegible]



ig. 7 a) Conventional tomogram. b–e) Series of 100-mm tomofluorograms of a dry skull in which an absolutely straight metal wire was inserted between the internal acoustic meatuses In (a) the wire is sharp at all points whereas in (b) only the middle part and in c) the both ends are sharp The object level height difference between b) and c) is 4 mm The tomographic angle was 31 In d) and e) the corresponding images obtained with the angle of 10 are only minimally blurred from the same sites The length of the wire is 60 mm Also in clinical situations the recognition of the form of the section will be of importance

n any case the basic concepts must be illustrated in some way otherwise there would be no geometry at least not tomographic geometry

Some geometric correlations between the sharp image areas (r z) the section thickness (d) and the radius of the ball surface of the input phosphor (R) are presented in Fig 6 DÜMMLING (1974) has remarked that the input phosphor of the Sirecon 17 H tube is not a strictly spherical surface but a slightly hyperboloid one An approximation has therefore been made in the figures with a spherical surface

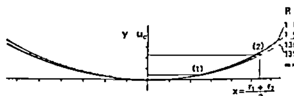


Fig 8 The curving of the section in I I tomography with Sirecon H 17 tube The p... produced experimentally using a sequential tomofluorographic method where a thin mesh was as an indicator of the object level, keeps most closely to an arc of 125 mm radius This is the value of R_0 of Fig 1 in present case A clear impression will be obtained if the figure is turned down If the x axis is thought to present an imaginary plane section the out-of plane pos... points (1) and (2) belonging to the spherical section are evident

In conclusion it may be stated that because of the geometry of the input ph... the conventional tomogram and the 100-mm tomofluorogram obtained from the same level of the object correspond only partially to each other with ... the common plane elements In the tomograms made by small an les there are ... of these common elements and the images have a greater mutual resembl... (Fig 7)

Tomofluorographic section

The detailed space geometric form of the tomofluorographic section was ... using the following method a thin metal mesh plate (100 meshes per cm² ... thickness 0 2 mm) was tomofluorographed at height intervals of *0 5 to 1 0* mm at a tomographic angle of 31 Thus first a small circular sharp image of the ... was obtained and then concentrical rings to the periphery of the 100-mm f... described in the previous chapter In every image the radius of the ring was m... and divided by 0 8 (M_t) Thus the corresponding millimeter values for the di... object levels (= u) and for the radial distances of the sharp rim zone (= $(r_1 - r_2)/2$ ... obtained The latter gradually increased as a function of the height shift from the zero point i e the height level at which the image plane runs tangentially to the cupola of the input phosphor (u = 0) The resulting points were drawn ... *ordinate system on millimeter paper (Fig 8) The line* connecting the p... represents an approximate cross-section of the section made by the Sirecon ... tube In probing experimentally it was revealed that an arc of a circl 125 mm in radius most closely resembled the final graphic result Now it was possible to calculate the radius of the approximate ball surface of the input phosphor ... according to the formula R_1 M_t R_o was 175 mm

In order to test the result obtained a steel wire 0 3 mm thick was bent ... to a millimeter paper pattern into a circular arc 125 mm in radius In t... grams (Fig 9) the wire remained in the sharp layer at all points The im... exposed with perpendicular movements and at a 45 angle to the l... of the wire When the test object was moved one millimeter out of the object plane the blurring of the image was homogeneous The full size tomogram of t...



Fig 9 An experimental proof for spherical section The views present the same steel wire of 0 3 mm thickness streched into form of an arc of 125 mm radius a) Conventional film b) tomogram c) 100-mm fluorogram d) 100-mm tomofluorogram with perpendicular and e–f) with 45 oblique transaxial movement In the tomofluorograms the wire is sharp at all points In (g) a homogeneous blurring appears when the wire is shifted one mm out of the former plane All tomofluorograms are made with an exposure angle of 31 Slight S curve of the wire in 100-mm films resulting from the influence of external magnetic field on image intensifier

object was then blurred in the same way as the straight wire in the 100-mm tomofluorogram The aim of these experiments was to find a clear illustration of the form of the tomofluorographic section and to reproduce it by tomography The spatial deviations of points (1) and (2) from each other and from the plane sectioned on the x axis are illustrated in Fig 8

Linear distortion and vignetting

Even the most modern electron-optic image transfer will cause some distortion of the object structures (FENNER 1965 FENNER & STAHKNE 1966 GEBAUER et coll 1974) In ordinary fluorography or in TV fluoroscopy the straight object lines are

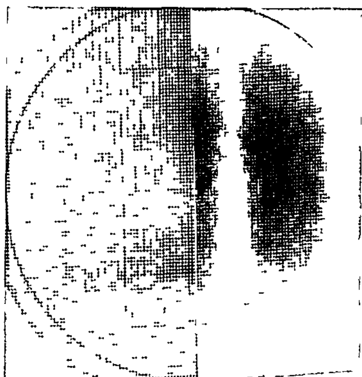


Fig 10 The mirror images of the same mesh halves a) Conventional film reduced to the size of [illegible] 100-mm fluorogram (b) is lacking the marginal disturbances—the vignetting and linear d[illegible] occurring in the latter

seen curving outwards at the image periphery—the usual form of linear distort[illegible] and some loss of luminance towards the image fringe—the vignetting—and the[illegible] phenomena occur in the tomofluorographic image as well DUMMLING (1974) [illegible] also remarked on the distortional effect of the earth s magnetism and of [illegible] brakes on the equipment These effects of the external magnetic fields on the [illegible] electrostatic field of the image intensifier although weak will crea[illegible] a s[illegible] S formed curve of the straight lines at the image center as well The occurrence a[illegible] the degree of the distortions caused by these three factors are evident in Fig 10 Th[illegible] mirror images of the same metal mesh are placed side by side on the le[illegible] ordinary film image is reduced to the size of the 100-mm fluorogram on th[illegible] The S formed curve also appears in the wire image in Fig 9 and is of th[illegible] degree in the tomograms so that the tomographic exposure per se does not call [illegible] any additional distortion in the linearity of the object structures

All three types of the distortion are significant mainly at image marg[illegible] beyond 80 to 85 per cent of the radial distance from the center (see also Gra[illegible] et coll 1974) Thus it may be concluded that the 100 mm tomofluorograph[illegible] will without major disturbances reproduce an area of some 100 mm in diamete[illegible] the object level This effective area would be increased to 145 to 150 mm b[illegible]

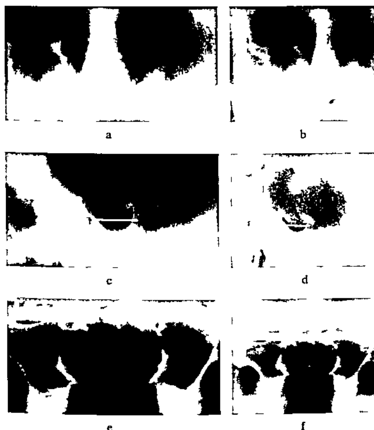


Fig 11 Comparative tomograms of dry skull details Exposure angle of 31
a c e) Conventional technique b d f) 100-mm technique

image intensifier with an input phosphor diameter of 250 mm assuming the other circumstances were the same

Significance of spheric section with areal limitation

In routine work thinking is channelled into plane geometry of the tomographic sections SOILA (1956) has shown using PAATERO s method of pantomography that deep layers can also be successfully tomographed with a technique where the section is much more curved It is therefore possible to claim that from the diagnostic point of view there will not be a decisive difference between the plane and slightly spherical section In many instances object details of small size are tomographed These include skull examinations solitary pulmonary and bone lesions the components of the biliary tract and local renal lesions Figs 11 and 12 demonstrate the similarity of the 100-mm and the plane sections It is almost impossible to observe essential

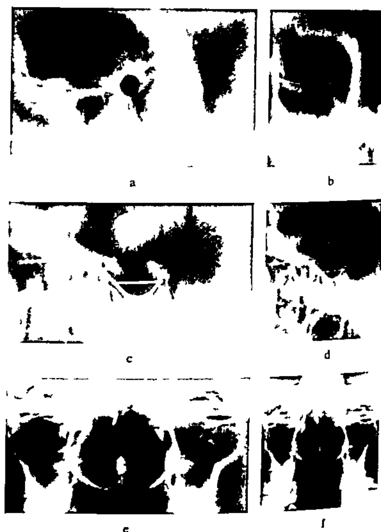


Fig 12 The same objects as in Fig 11 tomographed with an exposure angle of 10 a c e) Conventional technique b d f) 100-mm technique

differences in the object structures In view of the previous chapters it is obv that 100-mm tomofluorography with the small angle technique—zonogr is more suitable for those wishing to keep the plane section as a guiding pr However as MATTSSON (1972) stated Every tomographic examination m analysed by means of an adequate number of sections a single tomogram provides the whole truth Thus the structure details not included in o e se will appear in the adjacent sections and this principle is valid even in 100-m tomofluorograms made by larger angles when the comparative section ele differ more from those of usual tomograms of the same object level (Fig 7) Th counterparts of large field nasal sinus tomograms of the dry skull are sh



ig 13 The peripheral deviations between a) plane section—reduced standard tomogram—and) the spherical section—100-mm film The differences are most evident in the subtraction image (c) where the 100-mm section is curved more posteriorly in the supraorbital region (white contrary to black structures of the plane section)

ig 13 The conventional image was reduced to the size of the 100 mm film Then a masking film was made from the former and the latter was subtracted from it It is evident that the central parts of the images are identical The image periphery does not coalesce because it represents different object layers and because of the marginal distortion

No doubt the areal restriction of the 100 mm technique makes it unsuitable for wide survey tomography such as simultaneous examination of both kidneys during ...rography bilateral large field pulmonary tomography and especially the spinal canal examinations during gas myelography which demand absolute plane form of

Table 2

Comparison between exposure values in conventional tomography and various types of tomofluorography

Data from	Conventional tomography		Tomofluorography					
			Videotomo-fluorography		70-mm film		100-mm film	
	kV	mAs	kV	mAs	kV	mAs	kV	mAs
LASSER et coll (1971)	65	100	70	1 5				
	70	25	70	3 5				
KAUDE et coll (1973)	100	57			80*	15		
Present investigation								
Skull phantom	70	72					70	32
Enc lateral	70	100					70	50
Enc a p	75	140					75	80

* Without grid

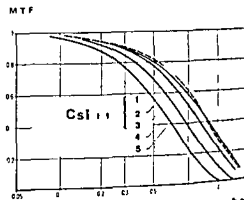


Fig 14 The modulation transfer function of CsI image intensifiers compared with an image intensifier of older type and a film screen combination (1) Sirecon 25/15 H without magnification (2) Sirecon 25/15 H with magnification (3) Sirecon 17 H (used in present experiments) (4) Sirecon 17 S with ZnS CdS input phosphor (5) Film screen combination (Universal screens) (Modified from GEBAUER et coll 1974 p 60)

the sections In utilizing image intensifiers with a larger input aperture (AD [illegible] 300 mm) the tomographic field size will increase though the minification ([illegible] $M_t \approx 0\ 30$) will reduce the resolution to a corresponding degree

Resolution ability

The new caesium iodide tubes have mostly proved of benefit to small [illegible] fluorography and cinefluorography The roentgen quanta absorption capa[illegible] of the input phosphor has improved from the previous 15 to 20 per cent to [illegible] per cent The MTF of the Sirecon 17 H tube is about 4 4 P/mm at the 4 per ce[illegible] contrast level equalling that of a film exposed between intensifying screens (Fig [illegible]) In this case the measurements were carried out on the surface and at the center of [illegible] input phosphor The resolution ability remains constant at a radial distance of [illegible] from the center and slowly slopes down to 90 per cent at the periphery Th[illegible] comparative results in the resolution power of 100 mm tomofluorography a[illegible] conventional film techniques appear in Fig 15 The test plate was placed on th[illegible] glass block 100 mm in thickness at an inclination of 45

Radiation dose

Small film fluorography dates from the fifties (JANKER 1954) The [illegible] interest in this method is due to the reduced radiation dose while diagnosti[illegible] tion still remains on an adequate level The ordinary conception is that th[illegible] film technique reduces the radiation dose to 1/10 to 1/5 KAUDE (1967) has s[illegible] 70-mm fluorography lowers the integral doses in the gastroduodenal exam[illegible] to 12 to 16 per cent As STIEVE (1961) has demonstrated the tomographic exp[illegible] deliver approximately the same doses as the exposures of ordinary ra[illegible] Thus it may be deduced that a considerable dose reduction can also be a[illegible] tomofluorography No comparative dosimetry was performed but the compa[illegible]

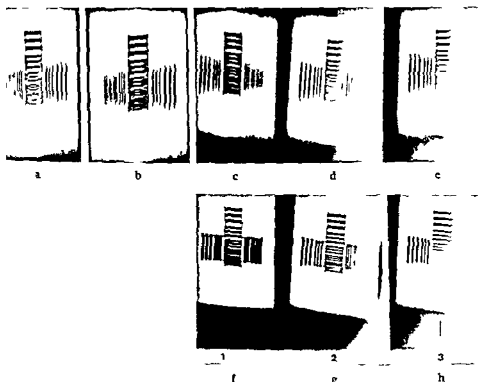


Fig 15 The resolution ability of 100-mm tomofluorography The test plate has been laid on the object level 45 inclined a) Standard film-screen combination with secondary grid and b) without grid Exposure angle of 31 c d e) 100-mm technique with exposure angles of 31 and f g, h) of 10 In the latter (c h) the plate has been placed so that the sharp image comes to the centre (1) and to the radial distances of 40 mm (2) and 70 mm (3) of the input phosphor The line pairs of 2 8 P/mm are clearly discernible at the central parts of 100-mm films The resolution falls to 2 0 P/mm in the image margin

Exposure rates given by LASSER et coll and KAUDE et coll appear in Table 2 as well as some of the present values All tomographies were made without the grid Efforts were made to keep the photographic density the same in the corresponding film pairs

Clinical application

In the tomography of metal objects and other phantom material with an excellent contrast the resulting images are of ideal quality In a clinical situation difficulties appear small contrast differences through thick tissue layers must be demonstrated In encephalography the contrast differences represent mean values Along with the development of neuroradiologic equipment tomography has become increasingly popular in the detailed analysis of the midline structures temporal horns and infratentorial structures At this hospital many pneumographic examinations are performed using 100-mm fluorography exclusively It has been found convenient to



Fig 16 In mid sagittal section the essential structures well discernible in 100-mm film (to the r[illegible]) Conventional film (to the left)

complete the examinations with tomography using the same camera After f[illegible] scopic centering it is easy to make successive tomograms without recurring c[illegible] changes Thus the clinical experience is based mainly on neuroradiologic exa[illegible] tions The distinctions between the conventional and the 100 mm techniques [illegible] evident in Figs 16 and 17 All the tomograms were made at an angle of 10 The central object planes are the corresponding ones i e the patient was [illegible] precisely 64 mm towards the image intensifier during the 100-mm tech[illegible] The tracheal bifurcation represents an object of weak contrast The quality of [illegible] 100 mm image is evident from a comparison of the film pair in Fig 18

The results suggest that the diagnostic quality of the 100-mm technique [illegible] satisfactory for the tomography of any human organ The spherical form and [illegible] limitation of the section make 100-mm tomofluorography unsuitable for large [illegible] examinations but in most instances tomography is directed selectively to d[illegible] an adequate size

Discussion

Most modern neuroradiologic and fluoroscopic equipment is provided [illegible] tomographic supplement and a televison chain Thus it is possible to make [illegible] fluoroscopy and tomofluorography after small technical adjustments Tom[illegible] scopy has previously gained some attention as a tomometric means. H[illegible] KAUDE et coll (1973) were the first to demonstrate small film tomofluor[illegible] as a method that could offset conventional tomography in clinical work [illegible] obvious that small film tomofluorography and tomofluoroscopy are compl[illegible] to each other It is easy to register the tomofluoroscopic information dir[illegible] spot film No complicated and expensive electronic arrangements are [illegible]

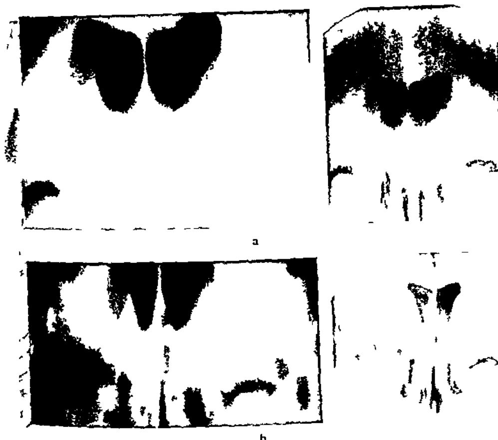


Fig 17 Conventional film to the left and 100-mm film to the right a) The left temporal horn and hippocampal details visible in 100-mm film (The conventional film unfortunately somewhat underexposed) b) An infratemporal expansion on the right 100-mm technique reveals the essential changes of the lateral ventricle and the minute shift of the third ventricle to the left (Centering the input lead marker may b n fit the evaluation of small midline shifts)

ima documentation particularly since the resolving power of these electronic methods in the present stage of the television technique is relatively poor The method described by DUMMLING is interesting and may be said to represent the first practical realization of analyzing the entire tomographic space image with one single exposure Most probably this method will bear fruit in the course of future technology The potential of the same method was realized already in 1960 by EDHOLM

Before small film tomofluorography is applicable to wider clinical use a clear understanding of the image characteristics must be gained The section is not a plane but is determined by the special features of the electron optic image transfer especially the features of the input phosphor The present results have demonstrated that the spherical form of the object section as such does not clearly diminish the

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ASPIRATION BIOPSY OF INTRAPELVIC METASTASES OF CERVICAL CARCINOMA

N EINHORN and J ZAJICEK

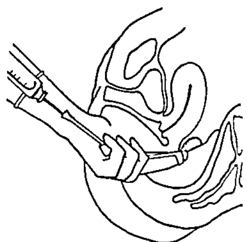
Metastases of carcinoma of the uterine cervix into lymph nodes in the pelvis ypogastric external iliac obturator parametrial paracervical and sacral nodes) in be anticipated in about 30 to 40 per cent of cases (HENRIKSON 1949) Digital xamination of a palpable pelvic lesion is highly unreliable as a diagnostic procedure malignancy is suggested microscopic confirmation is necessary Surgical b opsy to btain specimens for microscopy is technically difficult For this reason aspiration iopsy with a fine needle has been used at Radiumhemmet for many years to sample aterial for cytologic diagnosis

In order to evaluate the diagnostic usefulness of aspiration biopsy in advanced ervical carcinoma 316 cases were reviewed in which aspiration biopsy was per ormed on palpable intrapelvic lesions suggested to be metastases The cytologic indings were correlated with the clinical follow up The results are now reported and iscussed

Material and Methods

The 316 patients had primarily received radiation for carcinoma of the uterine ervix During the period 1966 to 1969 aspiration biopsy was performed due to uggested intrapelvic recurrence All were followed up for at least five years after he aspiration biopsy

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Sagittal section of the pelvis The needle inserted into a lymph gland

Fine needle biopsy The instrument was originally evolved for transrectal as[illegible] biopsy of the prostate (FRANZÉN et coll 1960) In most of the cervical carc[illegible] cases the transrectal approach was used (Figure) Transvaginal needling was d[illegible] only a few cases As a rule the aspiration biopsy was p rformed in g[illegible] anesthesia in connection with gynecologic examination Occasionally it was perf[illegible] in the out patient department without anesthesia The smears of aspirat[illegible] usually dried in air and stained with the May Grunwald Giemsa method In a f[illegible] cases methanol fixed Papanicolaou stained smears were also prepared

Results

In 55 of the 316 cases of treated cervical carcinoma in which intrapelvic le[illegible] suggested to be metastases were submitted to aspiration biopsy the c[illegible] report stated carcinoma In the remaining 261 cases the cytolog[illegible] examinati[illegible] not reveal malignancy In 37 of the 55 cases carcinoma was r ported at th[illegible] aspiration biopsy and in the other cases at repeat biopsy at subsequent visit[illegible] clinic No complications of the aspiration biopsy occurred

The five year survival rates among the patients with and those without mal[illegible] of the intrapelvic lesions are compared in the Table Of the 55 patients in [illegible] the aspiration biopsy showed intrapelvic spread of carcinoma 53 (96) d[illegible] malignant disease and only 2 survived for 5 years One of the 2 survivors [illegible] radiation therapy after the cytologic examination and the other was trea[illegible] cyclophosphamide Of the 261 patient with negative aspiration biopsy 101 ([illegible] died of malignant disease 27 (8) of intercurrent disease and 133 ([illegible] still alive after 5 years Of the 101 who died of malignant disease 60 [illegible] ically considered to have intrapelvic malignant growth

Table

[Cy]tologic findings in suggested intrapelvic metastases of cervical carcinoma and clinical follow up

[Fo]llow up 5 years after [asp]iration biopsy	Carcinoma		Negative		Total	
	No	Per cent	No	Per cent	No	Per cent
[De]ad of carcinoma	53	96	101	39	154	49
[De]ad of intercurrent disease			27	10	27	8
[Ali]ve	2	4	133	51	135	43
[To]tal	55		261		316	

Discussion

The accuracy of aspiration biopsy cytology in the diagnosis of carcinoma metas[ta]ses in lymph nodes is generally considered to be very high even in cases with [un]known site of the primary tumour The reasons for this are the abundant yield [of] cellular material and the ease with which metastatic carcinoma cells can be [di]stinguished from the normal constituents of the nodes In a series of 257 cases in [w]hich carcinomatous lymph nodes of the neck were examined by aspiration biopsy [a]nd subsequently excised for microscopy only 17 (7 per cent) received a false [ne]gative cytologic report (ENGZELL et coll 1971) Suggested reasons for the 17 [d]iagnostic failures were extremely small size of the target metastasis which therefore [w]as missed by the needle or that this metastasis developed after the aspiration [bi]opsy The interval between aspiration biopsy and extirpation of the node ranged [fr]om a few days to 12 months (ENGZELL et coll)

The present series consisted of 316 patients who following irradiation of carcinoma [o]f the uterine cervix underwent aspiration biopsy of palpable intrapelvic lesions [s]uggested to be malignant The cytologic report stated metastatic tumour growth in [5]5 cases and was negative in 261 During the follow up period 101 of these cytologi[c]ally negative patients (39 per cent) died of carcinoma and 60 of them were clinically [c]onsidered to have malignant growth in the pelvis The ratio of cytologically false [n]egative cases to cases given a definite cytologic report of malignancy thus was [6]0 55 If it is assumed that in all of the 60 cases with a negative cytologic report [m]etastatic tumour growth had occurred at the time of the aspiration biopsy the [d]iagnostic accuracy was only about 48 per cent Possible reasons for this relatively [l]ow figure were difficulties in the microscopic diagnosis or in collecting representative [c]ellular material

A review of the cytologic slides showed that the recognition of metastatic carcinoma [i]n the needle aspirates was not difficult The histologic type of the primary tumour [w]as known in all cases and as a rule carcinoma cells in vaginal smears were [a]vailable for comparison The risk of a false negative microscopic diagnosis [c]onsequently is negligible in such cases Also negligible is the risk of a false positive

report if the technique of collecting aspirate from the intrapelvic lesion is [illegible] factory When the transvaginal approach is used an inexperienced examiner [illegible] inadvertently aspirate benign squamous cells If these cells show irradiation dys[illegible] they may cause some diagnostic difficulty especially in cases of well differ[illegible] squamous cell carcinoma In the transrectal approach clusters of intestinal e[illegible] thelium may likewise be inadvertently aspirated and may present an inexpe[illegible] examiner with some difficulty particularly in poorly differentiated squam[illegible] carcinoma

Since the metastatic carcinoma cells were readily identifiable in the smears [illegible] false negative reports in the present series seemed to be ascribable to failure [illegible] obtain neoplastic cells Difficulties in selecting the target by palpation or in sa[illegible] cells from the area of malignant growth could both have contributed to this fa[illegible] Further, in some cases the carcinomatous growth may have developed after the needle biopsy Which of these three factors was mainly responsible for the diag[illegible] failures was not ascertainable since the palpable target area could not be ex[illegible] for microscopy The selection of targets for aspiration biopsy was based on cl[illegible] evaluation of palpatory findings The fact that 18 of the 55 cytologic reports [illegible] carcinoma were based on repeat, follow up biopsies suggests an improved selection [illegible] targets possibly due to progressive enlargement of the tumour area

The yield of malignant cells when a malignant lesion is aspirated depends m[illegible] upon the degree of fibrosis As a consequence of previous irradiation pa[illegible] intrapelvic metastases usually are fibrotic with transition to fibrosclerosis [illegible] hinders or prevents penetration by fine needles The yield at aspiration biopsy fr[illegible] such a fibrotic area usually consists of a minute droplet of cell free interstitial f[illegible] Connective tissue is not as a rule aspirated The question then arises if [illegible] findings are attributable to absence of tumour growth or to inability to a[illegible] carcinoma cells from sclerotic connective tissue With this in mind screw biopsy [illegible] recently introduced for lesions from which no representative material is a[illegible] with the fine needle The apparatus consists of a needle guide of the type us[illegible] transrectal aspiration biopsy and a needle containing a screw (about 0 5 mm [illegible] as devised by NORDENSTRÖM (1975) The screw method supplies fragm[illegible] connective tissue and it is highly probable that this technique will red[illegible] number of false negative reports The selection of the biopsy site will thus be [illegible] the main limiting factor in obtaining a cytologic diagnosis of intrapelvic [illegible] carcinoma

Following the cytologic diagnosis of intrapelvic metastasis 42 of the 55 p[illegible] received additional treatment—irradiation alone in 12 cases chemotherapy a[illegible] 19 cases irradiation plus chemotherapy in 10 cases and surgery in one case Th[illegible] most commonly used was cyclophosphamide A few patients received m[illegible] bleomycin or tifosyl Irradiation was usually given to a unilateral pelvic field [illegible] in doses of 30 to 50 Gy

This additional treatment did little to control the malignant growth [illegible]

the 45 patients survived for 5 years without clinical evidence of neoplasm. The futility of the lack of therapeutic response for secondary metastases of carcinoma of the uterine cervix has been pointed out by many (TA ELSEN 1949, MURPHY et coll. 1950, NOLAN coll. 1957, VAN HERIK & FRICKE 1959, KOTTMEIER 1959).

Although cytologic diagnosis of carcinoma cell spread within the pelvis did not contribute to prolonged survival of the patients, further improvement of the technique highly desirable. Correct assessment of the extent of the disease is a prerequisite for adequate care, particularly for testing new therapeutic measures against the advanced carcinoma.

SUMMARY

The findings at aspiration biopsy of palpable intrapelvic lesions were reviewed in 316 patients who had previously received radiation therapy for carcinoma of the uterine cervix. A cytologic diagnosis of malignant spread had been made in 55 cases. The crude five year survival rate in these patients was 4 per cent as compared with 51 per cent among the patients who received a negative cytologic report. Aspiration biopsy was positive in only about 48 per cent of the patients in whom follow up observations suggested intrapelvic spread of carcinoma. The factors that may have influenced the diagnostic accuracy are discussed. Use of a screw (0.5 mm thick) technique instead of the 22 gauge needle may enhance the diagnostic accuracy.

ZUSAMMENFASSUNG

Die Befunde bei der Aspirationsbiopsie von palpablen Veränderungen im Becken bei 316 Patienten die zuvor Strahlentherapie wegen eines Karzinoms der Cervix Uteri erhalten hatten werden berichtet. Die zytologische Diagnose einer malignen Ausbreitung wurde bei 55 Fällen gestellt. Die nichtkorrigierte 5 Jahres Überlebensrate bei diesen Patienten war 4 Prozent verglichen mit 51 Prozent bei Patienten mit einem negativen zytologischen Befund. Die Aspirationsbiopsie war nur in etwa 48 Prozent der Patienten positiv bei denen nach den späteren Beobachtungen eine Ausbreitung im Beckeninneren vermutet worden war. Die Faktoren die die diagnostische Genauigkeit beeinflussen können werden diskutiert. Die Verwendung einer Schrauben Technik (0.5 mm Dicke) anstelle einer 22 Gauge Nadel mag die diagnostische Genauigkeit verbessern.

RESUMÉ

Les resultats de la biopsie aspiration de lésions intrapelviennes palpables ont été revus chez 316 malades qui avaient éte traité pas les radiations pour un carcinome du col utérin. Le diagnostic cytologique de dissemination maligne a été fait dans 55 cas. Le taux brut de survie à 5 ans chez ces malades etait de 4% comparé avec 51% chez les malades dont l'examen cytologique était négatif. L'aspiration biopsie a été positive chez seulement 48% des malades chez lesquels l'évolution ultérieure a fait penser qu'il y avait une dissémination intrapelvienne du cancer. Les auteurs examinent les facteurs qui peuvent avoir influé sur la précision du diagnostic. L'utilisation d'une technique avec une vis (épaisseur 0.5 mm) au lieu d'une aiguille de calibre 22 peut augmenter la précision du diagnostic.

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INCREASED SERUM CALCITONIN IN PATIENTS WITH MAMMARY CARCINOMA

K J OLSEN C GADEBERG H E NIELSEN and A JOHANNSEN

Ectopic production of immunoreactive calcitonin (iCT) by lung and breast carcinomas has been demonstrated both in vivo (SILVA et coll 1974) and in vitro (COOMBES et coll 1976) This fact coupled with the finding that in patients with malignant diseases cases with bone metastases generally had elevated iCT levels compared with patients with local tumour (COOMBES et coll 1976 MILHAUD et coll 1976) suggests the use of iCT as a tumour marker and that iCT assays may play an important role in controlling the effectiveness of the treatment

However only little information is to be found about the relation between the clinical classification and the iCT levels in patients with malignancy Therefore iCT was measured in 40 cases of mammary carcinoma in which the extent of the disease was known and the results were compared with iCT in normals and with the values of 11 patients with benign mammary tumour

Material and Methods

The material consisted of 51 women aged 32 to 83 years (mean 55 7 years) admitted over an 8 month period with initial diagnosis of breast tumour All patients had normal kidney function and none had symptoms or signs of benign bone disease One patient was in treatment for pernicious anaemia Ten patients had previously

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been operated for mammary carcinoma and presented now with bone meta... In the remaining 41 patients the final diagnosis was based on microscopy of t... removed during operation Eleven patients had benign mammary tumour Th... patients with malignant tumour were classified according to the TNM system (UICC 1974)

The 51 cases were divided into the following groups

0 11 cases with benign tumours

1 16 cases with local malignant tumour

2 6 cases with metastatic spread to regional lymph nodes or to the skin

3 5 cases with primary malignant tumour and bone metastases

4 10 patients with bone metastases previously operated upon for mammary carcinoma

Three cases in whom the presence of metastases could not be determined w... certainty were excluded

All patients were examined preoperatively by whole body scanning wh... patients with proven carcinoma postoperative radiography of the skull sp... pelvis was performed

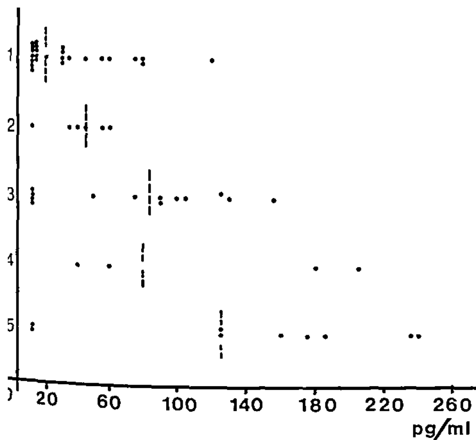
Fasting blood samples were obtained preoperatively for determination of se... calcium serum phosphorus alkaline phosphatase serum creatinine and serum ca... tonin

Calcitonin assay Immunoreactive calcitonin was determined in serum by the ra... immunoassay method of Dietrich et coll (1975) slightly modified The anti... to human calcitonin was supplied by Calbiochem USA The detection limit was ... pg/ml and upper normal level 120 pg/ml The precision was 10 pg/ml The inter... variation coefficient was 12 per cent at an iCT level of 140 pg/ml Further det... of the assay will be given elsewhere (Nielsen et coll 1978)

Statistical methods The Mann–Whitney U test for comparison of differences between group means and Spearman s rank correlation test were used

Results

The iCT levels in the groups with 3 and 4 (bone metastases) taken together appear in the Figure A group of normals is included for comparison One patient f... group 2 with an iCT of 365 pg/ml is left out since this patient was being trea... for pernicious anaemia No significant difference between serum calcitonin in gr... and the controls was found In group 1 the median level 85 pg ml was sig... higher than in the controls (p 0 02) but not significantly higher than the val... group 0 The patients in groups 3 and 4 had a median level of 125 pg ml wh... significantly higher than in group 1 (p 0 02) and normals (p 0 01) G...



rum calcitonin concentrations in controls (1) patients with benign breast tumour (2) with local alignant tumour (3) with regional metastases (4) and with bone metastases (5) Median levels in e groups are indicated

atients had a median level of 80 pg/ml which was significantly higher than the alues of group 0 (p<0 05) and normals (p<0 02) but not significantly different om groups 3 and 4 and group 1 The 3 patients who could not be placed in any of e groups had iCT levels of 40 85 and 205 pg/ml respectively

In groups 3 and 4 two patients had osteosclerotic bone metastases and iCT concen ations of 10 and 35 pg/ml respectively The other patients in groups 3 and 4 had steolytic bone metastases

Serum calcium concentration was normal in all patients except in one with osteo ytic metastases The serum calcitonin in this patient was 120 pg/ml Serum alkaline hosphatase was above normal range in one patient with benign breast tumour in ne with localized mammary carcinoma and in 6 with bone metastases No significant orrelation was found between serum calcitonin and serum concentration of calcium hosphorus and alkaline phosphata e

Discussion

Calcitonin is a small polypeptide hormone involved in the regulation of se[illegible] calcium and serum phosphorus by inhibiting bone resorption and increas[illegible] urinary excretion of these two ions (QUEENER & BELL 1975) The hormone is s[illegible] tised in C cells mainly in the thyroid gland In the most sensitive assays the n[illegible] level is reported to be lower than 100 pg/ml (ADACHI et coll 1976) Very high le[illegible] are found in medullary carcinoma of the thyroid (CLARK et coll 1969) In[illegible] levels have also been found in acute (ARDAILLOU et coll 1975) and chronic renal f[illegible] lure (SILVA et coll 1978 NIELSEN et coll) pernicious anaemia (FRANCHIMONT & HEYNEN 1976) trabecular carcinoma of the thyroid (MILHAUD et coll) and in [illegible] neoplastic conditions including lung and breast carcinoma (SILVA et coll 19[illegible] COOMBES et coll MILHAUD et coll)

The present results confirm that elevated iCT concentrations are quite co[illegible] in mammary carcinoma particularly in patients with metastatic spread of the d[illegible] Only 3 of 16 patients with localized tumours had increased iCT while 11 of 1[illegible] patients with bone metastases had increased calcitonin This is in agreement [illegible] the findings of COOMBES et coll who found that 23 of 28 patients with bone meta[illegible] had elevated iCT whereas only one of 13 with localized tumour had high iCT le[illegible] MILHAUD et coll found in a material of different types of malignant tumours [illegible] *only 50* per cent of patients with mammary *carcinoma and* bone metastases [illegible] elevated iCT The slight difference between these results is most probably d[illegible] differences in patient material

The cause of the elevated iCT levels may be either secretion by the tumour [illegible] physiologic response to osteolytic processes associated with bone metastases [illegible] low iCT levels in the 2 patients with osteosclerotic metastases support the h[illegible] hypothesis but ectopic production of iCT by mammary carcinoma have also b[illegible] demonstrated (SILVA et coll 1974 COOMBES et coll) The slightly elevated [illegible] level of iCT in patients with localized tumour compared with normals may be [illegible] to a physiologic response to osteolytic micrometastases COOMBES et coll found [illegible] iCT levels in 3 cases with mammary carcinoma *after mastectomy* One of th[illegible] developed bone metastases 3 months later This finding also supports the hyp[illegible] that elevated iCT is usually associated with osteolytic metastases The final de[illegible] about the two production mechanisms must await further analyses of iCT ch[illegible] following operation and other types of treatment

Regardless of the origin of the iCT production the present results indica[illegible] calcitonin assays may be of value in controlling the effectiveness of the t[illegible] and in particular indicate the presence of osteolytic bone metastases at [illegible] stage

Acknowledgements

This investigation was supported by the Danish Medical Research Coun[illegible] Synthetic human calcitonin was kindly supplied by Ciba Switzerland

SUMMARY

Serum calcitonin war within normal range in 11 patients with benign breast tumour In ises with local malignant breast tumour increased calcitonin was found in 25 per cent 4/16) in cases with regional metastases in 40 per cent (2/5) and in cases with osteolytic one metastases in 77 per cent (10/13) Two patients with osteosclerotic bone metastases ad low calcitonin concentration It is suggested that increased calcitonin in mammary arcinoma is a physiologic response to osteolytic bone metastases

ZUSAMMENFASSUNG

Serumcalcitonin war innerhalb eines Normalbereiches bei 11 Patienten mit benignen rusttumoren In Fallen mit lokalen malignen Brusttumoren stieg das Calcitonin in 25 Prozent (4/16) der Falle in Fallen mit regionalen Metastasen in 40 Prozent (2/5) und in Fallen mit osteolytischen Knochenmetastasen in 77 Prozent (10/13) Zwei Patienten mit osteosklerotischen Knochenmetastasen hatten eine niedrige Calcitoninkonzentration Das gesteigerte Calcitonin bei dem Mammakarzinom ist wahrscheinlich eine physiologische Antwort auf osteolytische Knochenmetastasen

RESUME

La calcitonine serique etait dans des limites normales chez 11 malades atteintes de tumeur benigne du sein Dans des cas de tumeur maligne localisee du sein on a trouve une elevation de la calcitonine chez 25 pour cent des malades (4/16) dans les cas de métastases regionales dans 40 pour cent (2/5) et dans les cas avec des metastases osteolytiques dans 77 pour cent (10/13) Deux malades ayant des métastases osseuses osteosclerotiques avaient une faible concentration de calcitonine Les auteurs pensent que l elevation de la calcitonine dans le cancer du sein est une reponse physiologique aux metastases osseuses osteolytiques

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PARATHYROID HORMONE AND CALCITONIN IN SERUM OF PATIENTS WITH MAMMARY CARCINOMA

BENTE RASMUSSON KR ROESDAHL and P LINDGREEN

The causes of alteration in the metabolism of calcium in patients with malignant diseases especially carcinoma of the breast the lung the kidney and multiple myeloma are only partly known The most frequently recorded and clinically most important is hypercalcemia most often occurring in patients with bone metastases Prostaglandins and parathyroid hormone ectopically produced by the tumor tissue have been considered responsible for this hypercalcemia (OMENN et coll 1969 BENSON et coll 1974 SEYBERTH et coll 1975)

The serum concentration of calcitonin and parathyroid hormone the two hormones known to be involved in the calcium metabolism were measured in patients with carcinoma of the breast to determine if a relationship between bone metastases and these hormones exists

Material and Methods

On 34 patients (mean age 61 years range 30–86 years) with microscopically proven carcinoma of the breast examined in the out patients department at the Radium Centre in Copenhagen during the period April–November 1976 the following examinations were performed clinical examination including palpation of the thyroid gland calcium phosphate alkaline phosphatases calcitonin parathyroid hormone creatinine GOT LDH and bilirubin in the blood $^{99}Tc^{m}$ bone scintigraphy and

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skeletal radiography Patients who did not have bone metastases at the time of this primary examination were re examined by bone scintigraphy and radiography 8 to 14 months later None of the patients had bone diseases apart from bone metastases

None of the patients except one who received thyroidine because of hypothyroidism had former diseases of the thyroid and none of them had palpable tumours in the thyroid gland

Ten patients had drug treatment prednisone—4 anti oestrogen—3 cytostatics and desiccated thyroid—1

Radioimmunoassay of human calcitonin Antibodies were prepared in rabbits by immunizing with synthetic human calcitonin M (CIBA) emulsified in Freund's complete adjuvant The rabbits received injections twice monthly the first two months then once a month Each injection contained 100 µg of calcitonin The animals were bled 14 days after the fourth and subsequent injections The blood selected for the assay had a binding constant (Scatchard plot) of 3×10^{10} l mol The final antibody dilution in the assay was 1 112 000 At this dilution 25 of the labelled calcitonin was bound

Synthetic human calcitonin M (CIBA) was iodinated by the chloramine-T method of GREENWOOD & HUNTER (1963) The product was purified by adsorption to QUSO G 32 and re eluted with acetone 40 % in acetic 2 % as described by YALOW & BERSON (1966) The tracer was further purified by gel filtration on a Sephadex G 50 column

Synthetic human calcitonin M (code No 70/234 Medical Research Co England) was used as a standard covering the range 0 050 to 3 2 ng/ml

A nonequilibrium radioimmunoassay was used in which standards and unknowns were incubated for 4 days at 4 C followed by the addition of 17 000 cpm ^{125}I of labelled calcitonin per tube After one further day of incubation the antigen-antibody complex was separated from the free antigen by precipitation with a second antibody (swine anti rabbit IgG)

The intra and inter assay reproducibility were 0 010 and 0 024 µg/l respectively for values less than 0 40 µg/l Above this value the intra and inter assay coefficients of variation were 5 8 and 8 per cent respectively

Dilution curves of human medullary carcinoma were superimposable with the inhibition curve obtained with MRC standard 70/234 Bovine parathyroid hormone (MRC standard 71/324) in concentrations up to 4 µg/l did not inhibit the binding between synthetic human calcitonin and the antiserum

The serum calcitonin concentration in all of 95 healthy subjects was less than 0 10 µg/l Of those 63 per cent had values less than 0 05 µg/l which is considered the limit of detection

Serum calcitonin concentrations were measured in 11 patients with medullary carcinoma of the thyroid In 2 patients radically treated for thyroid carcinoma

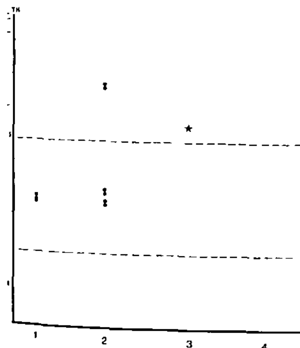


Fig 1 PTH levels The asterisk indicates the patient without bone metastases at the time of the first examination who however developed osteosclerotic metastases within 14 months 1 = No bone metastases 2 = osteolytic 3 = osteosclerotic, 4 = mixed osteolytic and osteosclerotic metastases

with no signs of recurrent disease the values were < 0 05 μg/l and 0 1 μg/l The lowest value in patients with known residual tumor was 1 35 μg/l The highest value 22 μg/l was measured in a patient with disseminate tumor in the neck

Radioimmunoassay of parathyroid hormone (PTH) Serum PTH was measured with a double antibody technique The antiserum was raised in a rabbit by immunization with a crude bovine parathyroid gland extract (parathyroid TCA powder Sigma) The antibody does not react with synthetic human PTH (1–34) (kindly supplied by P Riveille) indicating that the antibody is directed against the C terminal end of the PTH module The final antibody dilution used in the assay was 45 000

Highly purified bovine parathyroid hormone obtained from Wilson Laboratories Chicago was used for iodination (^{125}I) The iodination was carried out by the chloramine T method of GREENWOOD & HUNTER The tracer was further purified by adsorption to QUSO G 32 followed by elution with acetone 40 % /acetic acid 2 Finally the product was gelfiltrated on a Sephadex G 50 column

The standard used was the 1st International Reference Preparation of Bovine Parathyroid Hormone (code No 71/324 Medical Research Council)

The interassay SD was 0 035 μg/l in PTH < 0 70 μg/l and 8 9 in PTH > 0 70 μg/l and the intrassay was 0 012 μg/l Both apply to the normal range 0 22–0 50 μg/l in 03 normal subjects

Table

Parathyroid hormone and calcitonin concentration in serum related to bone involvement and to the type of bone metastases

	No of cases	PTH μg/l		No of cases	Calcitonin μg/l
		Mean	Range		
With bone metastases					
Osteolytic	17	0 46	0 30–0 77	1	0 34
				1	0 09
				1	0 08
				14	0 05
Osteosclerotic	5	0 59	0 42–0 77	1	0 09
				4	0 04
Mixed osteolytic and osteosclerotic	4	0 40	0 31–0 49	1	0 05
				3	0 04
Total	26	0 48	0 30–0 77		
No bone metastases	8	0 36	0 24–0 48	8	0 05

Results

Twenty six patients had bone metastases 17 osteolytic 5 osteosclerotic a 4 mixed osteolytic and osteosclerotic

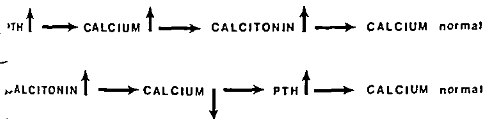
Parathyroid hormone Of 9 patients with PTH above normal level 8 patients had bone metastases (Fig 1) One patient with no bone metastases at the initial examination developed these in the skull and lumbar spine 14 months later Calcium concentration in the serum remained normal in this patient

Calcitonin One patient with osteolytic bone metastases had raised calcitonin in serum and the PTH measured 0 71 μg/l in this patient (Table)

Calcium Mean value of serum calcium was in the group without bone metastases 2 39 mmol/l (range 2 16–2 64 mmol/l) in the group with bone metastases 2 41 mmol/l (range 1 99–2 61 mmol/l) The normal range is 2 20–2 70 mmol/l

Other laboratory examinations Within the group of patients with bone metastases alkaline phosphatases were raised above the normal range (50–300 U/l) in 14 patients of whom 3 had raised PTH

Serum phosphate was raised in 3 patients with bone metastases 1 54 1 55 1 [illegible] mmol/l (normal range 0 80–1 50 mmol/l) PTH in these patients were 0 77 [illegible] and 0 43 μg/l respectively while serum-calcium measured 2 39 2 30 and 2 66 [illegible] GOT and LDH were slightly elevated in 2 patients None of them had other signs of liver metastases



ig. 2. Possible mechanisms for developing normocalcemic hyperparathyroidism. Upper row PTH is rimarily produced by the tumor Lower row Calcitonin is secreted in higher than normal amount ther by the tumor tissue itself or by the c-cells in the thyroid gland as a result of hypercalcemia iduced by the bone destruction

The serum-creatinine was normal in all patients Creatinine clearance was cal ulated according to the method of KAMPMANN et coll (1974) to exclude a decrease i renal function as the cause of an elevated PTH in the serum It was found to be ormal in all of the patients with raised serum PTH

Previous irradiation to the neck In addition to the surgical treatment for the rimary tumor 22 patients received irradiation to the thoracic wall axillae and upraclavicular region implying that a certain dose must have also been given to the arathyroid glands According to the doses given and the field arrangement the adiation dose to the homolateral parathyroid glands was estimated to between 31 nd 44 Gy and to the contralateral parathyroid glands between 2 4 and 7 Gy The nterval from irradiation to PTH measurement was between 6 months and 18 years mean 4½ years

In 5 patients with elevated PTH (0 52 0 64 0 65 0 70 0 76 μg/l respectively) the nterval from irradiation to PTH measurement varied between 6 months and 4 years n the irradiated group the mean PTH was 0 44 μg/l (range 0 27-0 76) in the non rradiated group 0 47 μg/l (range 0 24–0 77)

Discussion

The concentration in blood of immunoreactive parathyroid hormone has previ ously been measured in only a few patients with mammary carcinoma COOMBES et coll. (1976) found increased PTH in one of twelve patients and this patient had hypercalcemia

It has recently been demonstrated that malignant breast tissue can produce either PTH or some PTH analogue substance (MAVLIGIT 1971) and likewise COOMBES et coll (1975) have found that mammary carcinoma tissue contains immunoreactive calcitonin

Nine (35) of the 26 patients with bone metastases had PTH above the normal range This could be due either to a primary ectopic hyperparathyroidism (pseudo-

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was significantly higher in 26 patients with bone metastases than in 8 patients without (p<0 025) One patient with bone metastases had slightly raised calcitonin in serum No difference as to parathyroid hormone values between the groups of previously irradiated and non irradiated patients was found A possible explanation of the normocalcemic hyper parathyroidism is presented

ZUSAMMENFASSUNG

Das immunoreaktive Parathyreoidea Hormon und Calcitonin im Serum von 34 normo calcämischen Patienten mit Mammakarzinom wurde untersucht Der Mittelwert des Para thyreoidea Hormons war signifikant erhoht bei 26 Patienten mit Knochenmetastasen im Vergleich zu 8 Patienten ohne Metastasen ($p < 0\ 025$) Ein Patient mit Knochenmetastasen hatte ein leicht erhohtes Calcitonin im Serum Keine Unterschiede hinsichtlich der Para thyreoida Hormonwerte zwischen den Gruppen vorbestrahlter und nicht bestrahlter Pa tienten wurde gefunden Eine mogliche Erklarung des normocalcamischen Hyperpara thyreoidismus wird gegeben

RESUME

L'hormone parathyroidienne immunoreactive et la calcitonine serique ont ete mesurees chez 34 malades normocalcémiques atteints de cancer du sein Le taux moyen de l hormone parathyroïdienne est significativement plus éleve chez 26 malades ayant des metastases osseuses que chez les malades n en ayant pas ($p < 0\ 025$) Une malade atteinte de metastases osseuses avait une legere augmentation de la calcitonine serique Les auteurs n ont pas trouve de difference du taux d hormones parathyroïdiennes entre les groupes de malades irradies et de malades non irradies Ils présentent une explication possible de l hyperpara thyroïdisme normocalcemique

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FROM THE DEPARTMENT OF RADIATION THERAPY THE CENTER FOR ADULT DISEASES SAKA 537 AND THE DEPARTMENT OF RADIOLOGY OSAKA UNIVERSITY MEDICAL SCHOOL OSAKA 553 JAPAN

HIGH VERSUS LOW DOSE RATE INTRACAVITARY IRRADIATION OF CARCINOMA OF THE UTERINE CERVIX

A preliminary report

T INOUE S HORI Y MIYATA S OZEKI and Y SHIGEMATSU

Remotely controlled intracavitary radiation therapy with high dose rate was introduced to eliminate the radiation hazard to the staff members Nearly 70 sets of equipment had been installed in Japan by the end of October 1977 However the biologic effect produced by the high dose rate is not quite clear despite several reports on the clinical results from high versus low dose rate intracavitary irradiation for carcinoma of the uterine cervix At the present time various fractionation schedules are tested in the irradiation of carcinoma of the uterine cervix at various hospitals such as 3 Gy (300 rad) 3 times a week 5 Gy twice weekly 6 Gy once a week and 10 Gy once a week The total dose used varies between 28 and 36 Gy However the reports are difficult to compare as the clinical experience varies as well as technique and dosimetry Therefore it was considered motivated to compare high versus low dose rate intracavitary irradiation for carcinoma of the intact uterine cervix in a controlled series irradiated with uniform techniques

Materials and Methods

Shimadzu Ralstron 20A was installed in Osaka University Hospital in 1974 From October 1974 through March 1977 75 patients with squamous cell carcinoma

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of the intact uterine cervix were treated with Ralstron with or without 6 MV roe rays 64 were treated with intracavitary ^{137}Cs also with or without 6 MV roe rays In the high dose rate group the age ranged from 38 to 82 years with a m a age of 62 Four patients were classified in stage I 21 in II 45 in III and 5 in IV L the low dose rate group the age ranged from 35 to 80 years with a median age of 6 Eight patients were classified in stage I 18 in II 36 in III and 2 in IV The ages of the patients and the stage classification were compared and no statistical differen was found between the two groups

The treatment modality was as follows In the high dose rate group the stage IA cases were given a point A dose of 40 or 50 Gy in 4 or 5 fractions over 4 or 5 weeks with Ralstron alone The stage I B and II A cases were given 50 Gy in 5 fractions over 5 weeks with Ralstron and a mid plane dose of 30 Gy in 15 fractions over 3 weeks with central shield (4 cm in mid plane) using 6 MV roentgen rays The stage II B a d III cases were given 30 Gy in 3 fractions over 3 weeks with Ralstron and 20 Gy in 10 fractions over 2 weeks to the whole pelvis and thereafter 20 Gy in 10 fractions over 2 weeks with central shield using 6 MV roentgen rays In the low dose rate group the stage I A cases were given a point A dose of 60 Gy over 100 hours w th a 5 day gap using ^{137}Cs tubes The stage I B and II A cases were given 70 Gy over 120 hours with a 5 day gap using ^{137}Cs tubes and a mid plane dose of 30 Gy in 15 fractions over 3 weeks with central shiled using 6 MV roentgen rays The sta e II B and III cases were given 60 Gy over 100 hours with a 5 day gap using ^{137}Cs tubes and 20 Gy in 10 fractions over 2 weeks to whole pelvis and thereafter 20 Gy in 10 fractions over 2 weeks with central shield using 6 MV roentgen rays

Ralstron included 6 sets of ^{60}Co sources and generally 3 of them were used Th tandem source had a nominal activity of 148 GBq (4 Ci) ^{60}Co and each ovoid 4 GBq (2 Ci) in March 1974 By the automatic over ride system of the tandem source the treatment steps and time were selected in each patient (FODOR et coll 19 6) The dose rate in point A was varied from 1 to 1 5 Gy per min The tandem sources of the ^{137}Cs tubes had an activity of 1 39 GBq (37 5 mg Ra eq) and ovoids 1 11 GBq (30 mg Ra eq) The dose rate in point A was varied from 0 4 to 1 1 Gy per hour

In the high dose rate group a vaginal retractor (JOSLIN et coll 1977) was used f r protection of the anterior rectal wall Rectal dose was measured by the new device of ICD 5 (semi conductor dosimeter) (INOUE et coll 1977) The point A dose was calculated by Arthronix PC 12 All patients were observed for at least 6 months

Results

Overall 2 year actuarial survival rates were 77 ± 14 per cent and 81 ± 17 per c in the high and low dose rate groups respectively Actuarial survival curves of hi and low dose rate groups appear in Figs 1 and 2 Twenty one patients had died the end of September 1977 In the high dose rate group 3 died from the prima tumor 2 from the primary tumor and distant metastases 2 from distant metastases

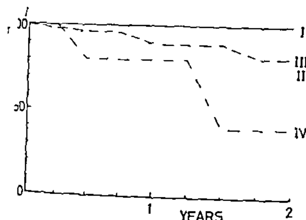


Fig 1 Actuarial survival curves for 75 patients with carcinoma of the uterine cervix treated with high dose rate intracavitary irradiation with or without 6 MV roentgen rays —— stage I (4) stage II (21) — — stage III (45) — — stage IV (5)

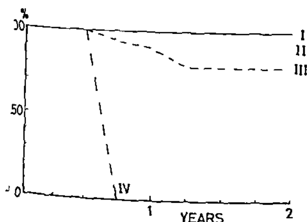


Fig 2 Actuarial survival curves for 64 patients with carcinoma of the uterine cervix treated with low dose rate intracavitary irradiation with or without 6 MV roentgen rays —— stage I (8) stage II (18) — — stage III (36) — — stage IV (2)

and 5 from intercurrent disease In the low dose rate group 2 died from the primary tumor 2 from the primary tumor and distant metastases 3 from distant metastases and 2 from intercurrent disease As to the survival rates and cause of death no statistical difference was found between the two groups

An analysis of the local condition of the irradiated area was done using the TDF factors (ORTON & ELLIS 1973 1974 ORTON 1974) (Fig 3) In the high dose rate group 3 of 4 patients with stage I cases were controlled and the fourth developed rectal bleeding Of 21 patients with stage II 17 were controlled one recurred and 3 developed rectal bleeding Of 45 patients with stage III 37 were controlled 4 recurred and 4 developed rectal bleeding Of 5 patients with stage IV cases 3 were controlled and 2 recurred In the low dose rate group 8 patients with stage I were controlled Of 18 patients with stage II 17 were controlled and one recurred Of 36 patients with stage III 29 were controlled 6 recurred and one developed rectal bleeding Two patients with stage IV cases recurred

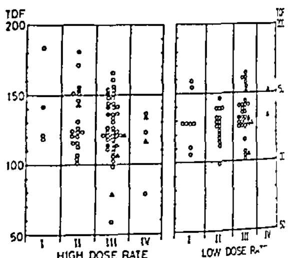


Fig 3 Local prognosis for 139 patients with carcinoma of the uterine cervix related to treatment method stage and time dose fractionation factors (TDF) ○ control ● rectal bleeding ▲ recurrence

Surgery was not indicated in any of the patients with rectal bleeding Such bleeding occurred more frequently in the high dose rate group than in the low one and continued more than 6 months in most cases A vaginal retractor was not used in 6 of the 8 patients with rectal bleeding in the high dose rate group due to the fact that no vaginal retractor was available before May 1975 The time dose fractionation factors (TDF) ranged from 59 to 183 with a median value of 123 and from 95 to 164 with a median value of 129 in the high and low dose rate groups respectively Depending upon the short term experience optimum TDF value was 125 in both groups

In the low dose rate group the point A dose was rather easily controlled because of the long irradiation time (about 50 h) In the high dose rate group each irradiation time was less than 10 min and the entire operation time was less than 40 min Accordingly the point A dose was estimated from standard display of dose distribution curves After the irradiation the point A dose was calculated with PC 12 in every case Accordingly in the high dose rate group the calculated point A dose differed highly from the planned dose Among 240 irradiations using Ralstron, the average point A dose was $10\ 03 \pm 1\ 31$ Gy (Fig 4) During the years an improved conformity was achieved and the calculated point A dose reached near the planned dose In the first year the average point A dose was $9\ 45 \pm 1\ 58$ Gy in the second year $10\ 38 \pm 1\ 15$ Gy and in the third $10\ 19 \pm 0\ 59$ Gy The standard display of dose distribution curves increased from 25 to 47 considering the separation between ovoids and length of the tandem source

Discussion

Various formulas have been proposed to equate high dose rate fractionated and low dose rate continuous irradiation LIVERSAGE s formula (1969) was based on the cell surviving fraction On the other hand TDF were based on the nominal standard

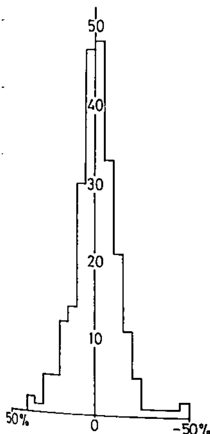


Fig 4 Per cent error between the calculated and planned point A dose in 240 irradiations with Ralstron Average point A dose was 10 03 ± 1 31 Gy

lose of high and low dose rate irradiation in clinical experience In this series the ffects of high and low dose rate irradiation were analysed using TDF Optimum TDF value was 125 both in high and in low dose rate irradiation in the present short erm experience

Recently clinical results of high dose rate intracavitary irradiation of carcinoma of the uterine cervix have been collected and analysed by some authors JOSLIN 1975) reported that 5 year survival rates were 90 57 and 42 per cent for stage I B I and III respectively ARAI & MORITA (1974) also obtained excellent results In he present series 2 year actuarial survival rates were 100 74 81 and 40 per cent or sta e I II III and IV respectively JOSLIN obtained an overall increase in 5 year urvival of 20 per cent in 345 patients treated with high dose rate intracavitary ir adiation The present results do not show any difference in survival rates between high and low dose rate irradiation

Rectal bleeding was observed more frequently in the high dose rate group than n the low one In an early period a vaginal retractor was not used and the calculated point A dose differed much more from the planned dose obtained from standard

dose distribution curve These two factors are probably the main cause of the frequency of rectal bleeding in the high dose rate group This will be discussed in the near future

SUMMARY

Overall 2 year actuarial survival rates were 77 and 81 per cent in a high and a low dose rate group respectively In the high dose rate group 60 patients were controlled, 8 de... rectal bleeding, and 7 recurred In the low dose rate group 54 were controlled, one developed rectal bleeding, and 9 recurred Optimum TDF was 125 in both groups

ZUSAMMENFASSUNG

Die Überlebensraten bei einer Gruppe mit hoher und einer mit niedriger Dosisrate ... 77 bzw 81 Prozent In der Gruppe mit hoher Dosisrate wurden 60 Patienten symptomfrei bei 8 entwickelte sich eine rektale Blutung und bei 7 ein Rezidiv In der Gruppe mit niedriger Dosisrate wurden 54 Patienten symptomfrei bei einem entwickelte sich eine rektale B... und bei 9 ein Rezidiv Die optimale TDF war 125 in beiden Gruppen

RESUME

Le taux actuariel global de survie a 2 ans a été de 77 pour-cent chez un groupe de malades atteintes de carcinome du col de l utérus et ayant reçu un taux de doses elevees et de ... pour-cent chez un groupe de malades ayant reçu un faible taux de doses D... taux de doses élevees 60 malades ont été guéries 8 ont presente une hemorragie recta... 7 ont recidive Dans le groupe à faible taux de doses 54 malades ont ete gueries, une ... une hemorragie rectale et 9 ont recidivé Le meilleur facteur de fractionnement de la d... en fonction du temps a eté de 125 dans les deux groupes

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HLA ANTIGENS IN HODGKIN S DISEASE OF VERY LONG SURVIVAL

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Deepened understanding of the biodynamics of Hodgkin s disease and better methods for determination of the extent of the disease and its treatment have resulted a great improvement in prognosis over th last 10 years With the restricted diag stic and therapeutic measures available in th 1960 s a 5 year survival rate of 22 r cent was reported (EASSON & RUSSEL 1963) With modern staging and t eatment day a 5 year survival rate of at least 70 per cent for all patients has been reported APLAN 1972) In order to reach such high survival figures it has usually been cessary to employ intensive radiation therapy or intensive chemotherapy At the esent time it is not cl ar to what extent late adverse effects may counterweight the nef cial effects of the intensive treatment There is for instance increasing evidence at more in ensive combined therapy results in an inc eased frequency of secondary alignancies e g leukemia (CAVALIN STÅHL et coll 1977)

In recent years the interest has been concentrated on prognostic factors in Hodg in s disease for the purpose of enabling a more differentiated therapy

Among the well known prognostic factors in Hodgkin s disease may be mentioned inical stage (including systemic symptoms and signs) histologic type length of istory (stage by stage) leukocyte count ESR (WESTLING 1965) type of therapy nd age of the patient Th last mentioned factors may be an indicator of the de reased immunologic competence in high r age and it is well known that the im

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Overall 2 year actuarial survival rates were 77 and 81 per cent in a high and a low dose rate group respectively In the high dose rate group 60 patients were controlled 8 developed rectal bleeding and 7 recurred In the low dose rate group 54 were controlled one developed rectal bleeding and 9 recurred Optimum TDF was 125 in both groups

ZUSAMMENFASSUNG

Die Überlebensraten bei einer Gruppe mit hoher und einer mit niedriger Dosisrate waren 77 bzw 81 Prozent In der Gruppe mit hoher Dosisrate wurden 60 Patienten symptomfrei bei 8 entwickelte sich eine rektale Blutung und bei 7 ein Rezidiv In der Gruppe mit niedriger Dosisrate wurden 54 Patienten symptomfrei bei einem entwickelte sich eine rektale Blutung und bei 9 ein Rezidiv Die optimale TDF war 125 in beiden Gruppen

RESUME

Le taux actuariel global de survie à 2 ans a eté de 77 pour-cent chez un groupe de malades atteintes de carcinome du col de l utérus et ayant reçu un taux de doses elevees et de 81 pour cent chez un groupe de malades ayant reçu un faible taux de doses Dans le groupe à taux de doses élevées 60 malades ont été guéries 8 ont présenté une hémorragie rectale et 7 ont récidivé Dans le groupe à faible taux de doses 54 malades ont été gueries une a eu une hémorragie rectale et 9 ont récidivé Le meilleur facteur de fractionnement de la dose en fonction du temps a été de 125 dans les deux groupes

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HLA ANTIGENS IN HODGKIN'S DISEASE OF VERY LONG SURVIVAL

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Deepened understanding of the biodynamics of Hodgkin's disease and better methods for determination of the extent of the disease and its treatment have resulted in a great improvement in prognosis over the last 10 years With the restricted diagnostic and therapeutic measures available in the 1960 s a 5-year survival rate of 22 per cent was reported (EASSON & RUSSEL 1963) With modern staging and treatment today a 5-year survival rate of at least 70 per cent for all patients has been reported (KAPLAN 1972) In order to reach such high survival figures it has usually been necessary to employ intensive radiation therapy or intensive chemotherapy At the same time it is not clear to what extent late adverse effects may counterweight the beneficial effects of the intensive treatment There is for instance increasing evidence that more intensive combined therapy results in an increased frequency of second malignancies e g leukemia (CAVALIN STÅHL et coll 1977)

In recent years the interest has been concentrated on prognostic factors in Hodgkin's disease for the purpose of enabling a more differentiated therapy

Among the well known prognostic factors in Hodgkin's disease may be mentioned clinical stage (including systemic symptoms and signs) histologic type length of history (stage by stage) leukocyte count ESR (WESTLING 1965) type of the ... and age of the patient The last mentioned factors may be an indicator of the decreased immunologic competence in higher age and ... is well known that the im...

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Table 1

Sex age microscopic type stage and length of follow up in 40 patients with Hodgkin s disease

	10 long survivors	30 patients untreated or with only short follow up
Male female	3 7	22 8
Age (years) range	15-52	15-78
mean	(29)	(36)
Microscopy		
Lymphocyte predominance	1	6
Mixed cellularity	2	8
Lymphocyte depletion	0	4
Nodular sclerosising type	7	12
Stage		
I	4	10
II	5	9
III	0	7
IV	0	4
II_e	1	0
Follow up (years) range	18 9	0-10
mean	(23)	(?)

munologic status of patients with Hodgkin s disease has prognostic implication (HOLM et coll 1976)

In experimental systems it has been demonstrated that the survival of mice who developed leukemia after infection with the Gross virus was dependent on th type of the major transplantation antigens (H 2 LILLY et coll 1964) In man extensive investigations have been performed for many different diseases includin tumors of the relationship if any between the HLA system and clinical parameters and prognosis

However the findings on HLA in Hodgkin s disease in different series have been partly contradictory (SVEJGAARD et coll 1975) Usually untreated patients have been examined and thus correlation if any between the HLA system and prognosis has not been fully explored

The present report analy es the HLA system in a group of patients with Hod kins disease some of whom were very long survivors

Material and Methods

A report was given in 1973 (LANDBERG & AHLSTRÖM) on 13 patients with H kin s disease who had survived at least 15 years after treatment Since the diagnostic and therapeutic methods that had been used in these patients had been when viewed

Table 2

HLA types determined in 40 patients with Hodgkin s disease and in 1 6?3 normal subjects

A	B	C
1	5	w1
2	7	w2
3	8	w3
9	12	w4
10	13	
w25	14	
w26	15	
11	w16	
w19	w17	
w29	w18	
w32	w21	
28	w22	
	27	
	w35	
	w37	
	w40	

modern concepts very limited these patients may be considered to have had ...her a benign form of Hodgkin s disease or a good reaction toward the disease Of ...e 13 patients 8 were alive at the time of the 1973 investigation and were tested for ...LA type A further two patients with very long symptom free survival were also ...cluded in the present material thus consisting of 10 patients all of whom had ...en symptom free after the initial treatment and then been followed for mean 23 ...ars Further information on the 10 long survivors is given in Table 1

...Another series consisting of 30 patients with Hodgkin s disease was also tested for ...LA type Thirteen were consecutive new patients admitted during 1973 and 17 ...ere follow up cases the same year (Table 1)

...HLA typing of the 40 patients was done in 1973 according to a microlymphocyto...xicity test (KISSMEYER NIELSEN & KJERBY 1973) Thirty two different HLA types ...the A B and C series were determined (Table 2)

The distribution of the HLA types in 1 263 normal subjects served as a reference

Results and Discussion

Significant differences between different subgroups of patients with Hodgkin s ...isease and the reference group with respect to distribution of HLA types is given ...n Table 3 The patients with Hodgkin s disease have been divided into (1) all 40 ...atients (2) 10 long survivors and (3) 19 patients with nodular sclerosing type The

Table 3

Significant differences between different subgroups of patients with Hodgkin s disease and a reference group of normal subjects with respect to distribution of HLA types p-values according to the chi square test with Yates correction

HLA	Reference group	All 40 patients	10 long survivors	19 with nodular sclerosing type
A 28	87 1263 (7)		3 10 (30 p < 0 05)	
B 18	63/1263 (5)	8 40 (20 p 0 001)		5 19 (26 p < 0 0)

reason for listing nodular sclero ing type separately is the existence of th spe morphologic clinical and prognostic characteristics of this type indicatin that the subgroup may be basically different from the other types

In all patients with Hodgkin s disease not subdivided according to follow up or histology HLA B18 occurred more frequently than in the reference group Th same finding was made for the subgroup of 19 patients with nodular sclerosing disease but not for the subgroup of 10 long survivors An increased frequency of HLA B in Hodgkin s disease has also been reported by AMIEL (1967) SVEJGAARD et al and BJÖRKHOLM et coll (1975)

The 10 long survivors (Table 3) but not the entire group of 40 pati nts or the s group of those with the nodular sclerosing type had an increased frequency of HLA A28 Such an increase has also recently been reported by HANSEN et coll (19) who however presented no long term data The finding of an increased frequ ncy of HLA A28 in patients with apparently good prognosis is contradictory to the finding made by BJÖRKHOLM et coll who suggested that HLA A28 may be asso ciated with advanced disease and poor prognosis

HLA A1 has previously been reported to be frequently encountered in Hodgkin s disease Thus HENDERSON et coll (1973) often found HLA A1 in patients with Hodgkin s disease without correlation to histologic typ KISSMEYER NIELSEN et coll also found HLA A1 to be frequent in Hodgkin s disease and also emphasized the association between HLA A1 and HLA A8 Subdivision according to histology in their series showed that HLA A1 and HLA A8 had the lowest frequency in patients with the nodular sclerosing type and the highest in patients with mixed cellularity Further a correlation with age was found patients over 30 years of age often having HLA A1 and HLA A8 The results in their series were drawn from untreated patients However in a prospective investigation BJORKHOLM et coll found that the distribution of HLA types in patients with Hodgkin s disease was not different from that of healthy controls In the present series HLA A1 occurred in about 40 per cent of all 40 patients with Hodgkin s disease and in about the same percentage of the 10 long survivors compared with the figure 29 per cent for the reference group the differences not being significant This observation corresponds to that of BJÖRKHOLM et coll

One may specula e that the very long survival in the p esent 10 pati nts despite y limited staging procedures and limited therapy implies that these patients had ood defence towards the disease The finding of an increased frequency of HLA 8 may then d spite the small material be of some importance when evaluating nosis It should be emphasized that when performing the statistical analysis it s decided not to perform simultaneous inference Therefore even in the complete ence of any true difference 1 5 significant differences will be exp cted at the level 5 when p rforming 32 s parate tests

Apparently HLA typing in Hodgkin s disease has been reported to yield varying ults One explanation may be differences in the composition of the patient series ecially with respect to the length of follow up

Acknowledgement

The authors express their thanks to Dr Carl Johan Lamm for the statistical analysis

SUMMARY

Determination of 32 different HLA types in the A B and C series was performed in 40 tients with Hodgkin s disease 10 of whom had a very long survival A group of 1 263 althy subjects was used as reference HLA B18 was seen significantly more often in all 40 tients and also in the subgroup of patients with nodular sclerosing Hodgkin s disease An reased frequency of HLA A28 was observed among the 10 long survivors but only with ak significance

ZUSAMMENFASSUNG

Bestimmungen von 32 verschiedenen HLA Typen in den A B und C Gruppen bei 40 tienten mit Hodgkinscher Erkrankung wurden durchgeführt von denen 10 eine lange berlebenszeit hatten Eine Gruppe die 1 263 gesunde Personen umfasste wurde als Re renz verwendet HLA B18 fand sich signifikant häufiger in allen 40 Patienten und eben ir in der Untergruppe von Patienten mit nodularer sklerosierender Hodgkinscher Krank it Ein Anstieg in der Frequenz von HLA A28 wurde bei den 10 lang Überlebenden ge rden, jedoch nur mit einer schwachen Signifikanz

RESUME

La determination de 32 types HLA differents dans les series A B et C a eté faite chez malades atteints de maladie de Hodgkin dont 10 avaient une survie tres longue Un groupe 1 263 sujets normaux a été utilisé comme reference On a trouve une frequence significa vement plus elevee de HLA B18 chez ces 40 malades et aussi dans le sous groupe de ma des qui avait une maladie de Hodgkin nodulaire sclerosante On a trouve aussi une fre uence augmentee de HLA A28 parmi les 10 malades ayant une longue survie mais avec ulement une faible signification

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HODGKIN S DISEASE TREATED BY CHEMOTHERAPY AND LARGE FIELD IRRADIATION

Hematologic effects

H EGHBALI G HOERNI SIMON M DURAND J CHAUVERGNE
J TOUCHARD and B HOERNI

Since 1965 following the Symposia of Paris (1966) and of Rye (1966) radical idiation therapy has been recognized as the main treatment of patients with Hodgkin s disease stage I and II However the usefulness of combining chemotherapy with irradiation in the treatment of these types of Hodgkin s disease has been recently demonstrated by many groups (E O R T C 1972 LAGARDE et coll 1975 ROSENBERG & KAPLAN 1975) Various types of chemotherapy have been used Nevertheless is sometimes difficult to combine the two types of treatment particularly concerning the tolerance of the patient In order to determine the hematologic effects of such a combination a homogeneous series of patients was analyzed which had been treated according the same schedule of chemotherapy–irradiation–chemotherapy during the past 8 years at the Fondation Bergonie (HOERNI et coll 1977) The results are now reported

From January 1969 to October 1976 112 patients with clinical stage I and II of Hodgkin s disease were treated at this hospital Forty two patients were excluded from the analysis for the following reasons 11 patients had been treated prior to admission 6 had subdiaphragmatic disease 8 were irradiated but received only one cycle of chemotherapy for non medical reasons 6 received irradiation fractionated in two parts 5 were administered another type of chemotherapy than the usual one

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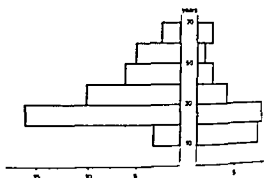


Fig 1 Age and sex of 70 patients (42 males, left 28 females, right)

4 were irradiated only due to their age and poor condition lastly 2 patients were treated elsewhere Seventy patients treated exactly according to the same schedule of combined irradiation and chemotherapy were thus suitable for the present analysis

Age and sex distribution appear in Fig 1 The microscopic types were distributed as follows 8 patients had type I (lymphoid predominance) 40 type II (nodular sclerosis) 20 type III (mixed cellularity) and 2 type IV (lymphoid depletion). In all patients the staging was performed according to the data of the Rye Symposium with a complete physical examination conventional chest radiography mediastinal tomography and abdominal lymphography When the lymphographic findings were uncertain (particularly for para aortic lymph nodes) they were always considered as not abnormal Neither exploratory laparotomy bone marrow biopsy nor splenectomy were performed All patients were followed up until their deaths, or until October 1977 none were lost

Treatment All 70 patients were treated according to the same schedule They received first one cycle of chemotherapy consisting of cyclophosphamide vinblastine procarbazine and methyl prednisolone (CVPP) (CHAUVERGNE et coll. 1973 Fig 1 The dosage of the drugs was usually the same for all patients and the treatment was given for a maximum of 21 days or until the leukocytes reached 2 000 per μl. However for some children or small patients (weighing less than 40 to 50 kg) the dose was reduced according to their weight

The irradiation as a rule followed chemotherapy immediately but the interval was in some cases a few days but never more than 6 days Except for 2 obese cases (in which supervoltage roentgen therapy was used) all patients received ^{60}Co irradiation The source skin distance was 100 to 120 cm The total dose was 40 Gy in the involved areas and 35 Gy in adjacent areas given alternately every other day to anterior and posterior fields in 4 weeks with 5 weekly fractions of 20 Gy The fields were designed according to the mantle technique with protection of lungs and upper extremities of the humerus and of the larynx for the anterior field. The spinal cord was protected for the posterior field when irradiated with more than 30 Gy In addition to mantle fields the lumboaortic region was irradiated simultaneously

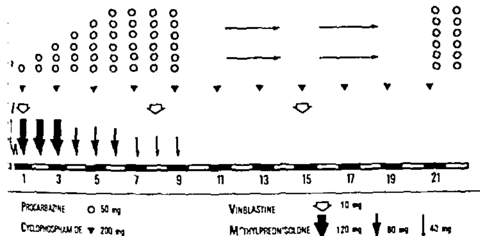


Fig. 2 Schedule of chemotherapy

ed according to the same schedule for all patients It is necessary to point out that for the mediastinum the fields were delineated after chemotherapy on the persisting abnormal lymph nodes and not on the initial involvement the width of fields in comparison with the initial width of the mediastinal node lesions was thus usually reduced at least for patients with involvement of the mediastinum

Lastly all patients received a second cycle of chemotherapy according to the same schedule This period of chemotherapy began after a rest of one month following the completion of irradiation the interval being on the average 34 days For 3 patients this interval lasted 2 months since their leukopenia remained uncorrected after one month of rest No maintenance treatment was given The hematologic effects were recorded by blood cell counts performed usually every other day during chemotherapy and weekly during irradiation After completion of the treatment period the patients were controlled every three months during the first year and then every 6 months The number of granulocytes and lymphocytes could not be followed because during the period of leukopenia the differential leukocyte counts were usually not performed Only 16 patients received transfusions of erythrocytes during irradiation and 13 during the second cycle of chemotherapy None received leukocytes or platelets The mean value of blood cell counts was calculated according to the analysis of variance

Results

The variation of blood cell counts appears in Figs 3 to 5

The erythrocytes varied very little with complete recovery 10 months after the beginning of the treatment (Fig 3)

The variations of leukocyte counts were more striking (Fig 4) The mean value of the initial count was above the normal values During each cycle of chemotherapy

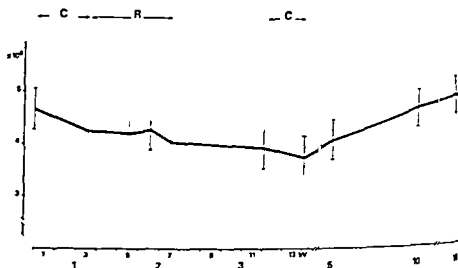


Fig 3 Variation of erythrocytes C = Chemotherapy R = Radiation therapy

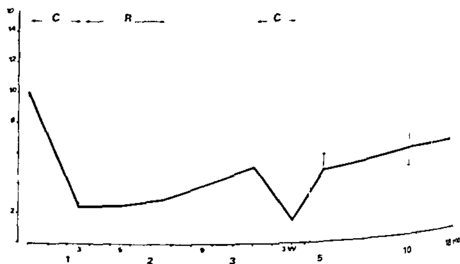
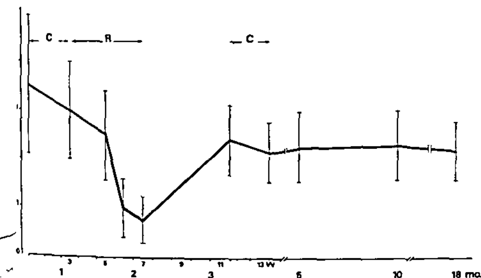


Fig. 4 Variation of leukocytes C = Chemotherapy R = Radiation therapy

the counts decreased to a mean value of 2 000 per μl Then they increased slightly but not significantly during irradiation This increase was more marked during the month of rest with an almost complete recovery to normal level A similar recovery had occurred two months after completion of the second cycle of chemotherapy Ten months after the beginning of the treatment period normal levels were attained

The platelets varied quite differently (Fig 5) Platelet counts dropped slightly during each cycle of chemotherapy but markedly during irradiation The recovery was good after the radiation therapy After the end of the overall treatment the



g 5 Variation of platelets C = Chemotherapy R = Radiation therapy

atelet level remained stable with an average value slightly inferior to the normal ne

Hemorrhagic complications were never observed but some infectious complica ons occurred (possibly enhanced by leukopenia) No complications were en ountered during the first cycle of chemotherapy nor during or after irradiation After the second cycle of chemotherapy 10 patients had fever 4 of them requiring o treatment and lasting no longer than 4 days 6 of them more marked and neces tating antibiotic therapy for one week In all these patients the leukocyte counts ere less than 1 000 per μl Neither the stage of the disease (I or II A or B) nor the istologic type seemed to influence this severe leukopenia Only 2 of these patients were more than 55 years old their average weight was 49 kg in comparison with 61 g for patients without complications Thus it appears that the schedule of chemo herapy usually guided by leukocyte count and not by weight or surface of the atients is responsible for these mild complications

Comments It appears from the preceding data that polychemotherapy and radia ion therapy may be combined and given during a short period according to a some what heavy schedule This conclusion may not be valid with another schedule than the one used in the present series and particularly with another type of chemo therapy The present results were obtained in patients who had not undergone splenectomy

The whole regimen applied was brief and also efficient as previously stated (LA GARDE et coll 1975) Many other regimens have been proposed for localized Hodg kin s disease but it is rather difficult to compare the present data to other series

because almost all other radiochemotherapeutic combinations were app[illegible] patients staged by surgical procedures and thus classified according to a p[illegible] and not to a clinical staging furthermore these patients are usually splenector[illegible]

From previous data it appears that the results obtained for these pa[illegible] particularly favorable (LAGARDE et coll) It should be emphasized that these r[illegible] were obtained after a particularly brief but intensive treatment which is not al[illegible] well tolerated Short term risks were rare and minor and furthermore they co[illegible] reduced by carefully adapting the chemotherapeutic dosage to each patient [illegible] no long term risk appeared at least judging from the hematologic effects.

Conclusion

The results show that patients with clinical Hodgkin s disease sta[illegible] I and II m[illegible] be treated with a combination of chemotherapy and irradiation witho[illegible] hematologic complication However the conclusion drawn is not necessarily [illegible] for other types of irradiation or chemotherapy

SUMMARY

The hematologic effects of combined chemotherapy and irradiation were analyzed [illegible] patients with Hodgkin s disease stage I and II The schedule used was as follows one [illegible] of 15–21 days of chemotherapy immediately followed by irradiation including m[illegible] lumboaortic fields After a rest of one month another cycle of the same chemother[illegible] applied The erythrocytes varied slightly the leukocytes decreased during chemother[illegible] and were stable or increased slightly during irradiation Platelets decreased slightly d[illegible] chemotherapy and more markedly during irradiation No major side effects were observed and the regimen appeared well tolerated

ZUSAMMENFASSUNG

Die hamatologischen Wirkungen der kombinierten Chemotherapie und Bestrah[illegible] wurden bei 70 Patienten mit Hodgkinscher Krankheit Stadium I und II analysiert. Da[illegible] verwendete Schema war folgendes ein Zyklus von 15 bis 21 Tagen Chemotherapie, m[illegible] mittelbarem Anschluss daran Bestrahlung umfassend Mantel und paraaortikale Fe[illegible] Nach einer Pause von einem Monat wurde ein weiterer Zyklus von derselben Chemotherapie verwendet Die Erythrozyten veranderten sich wenig, die Leukozyten fielen wahrend der Chemotherapie und waren stabil oder stiegen leicht wahrend der Bestrahlung. Die Th[illegible] zyten fielen leicht wahrend der Chemotherapie aber m hr markant wahrend der Bestra[illegible] Keine wesentlichen Nebeneffekte wurden beobachtet und das Regim wurde gut vertragen.

RESUME

Les effets hematologiques de la chimiothérapie associee à l irradiation ont été etudies chez 70 malades atteints de maladie de Hodgkin au stade I et II Le plan de traitement utilise a ete le suivant un cycle de 15 a 21 jours de chimiotherapie suivi immed[illegible] par l irradiation comprenant des champs en mantelet et lomboaortique Apres un mois

un mois un autre cycle de chimiothérapie a été administré Les érythrocytes ont peu varié les leucocytes ont diminué pendant la chimiothérapie et sont restés stables ou ont un peu augmenté pendant l irradiation Les plaquettes ont un peu diminué pendant la chimiothérapie et ont diminué de façon plus marquée pendant l irradiation Les auteurs n ont pas observé d effets secondaires important et ce traitement parait bien toleré

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^{67}GA-SUBTRACTION SCANNING IN HODGKIN S DISEASE AND LYMPHOMAS

H KROLIKIEWICZ Y MARUYAMA F H DELAND
R M BEIHN T HAFNER and E E KIM

During the last years a considerable interest has appeared in the staging of Hodgkin s disease (ROSENBERG 1966) and non Hodgkin s lymphoma using radionuclide methods ^{67}Ga being the most successful tumor detecting agent known to date It localizes well in both lymphoma and Hodgkin s disease as reported by EDWARDS & HAYES (1970) HIGASHI & NAKAYAMA (1972) GREENLAW et coll (1974) and JOHNSTON et coll (1977) but also localizes in inflammatory processes and abscesses (BEIHN et coll 1974) Recently a method was described in which ^{67}Ga subtraction scanning was applied to enhance tumor detection and tumor localization (DELAND et coll 1975) This method utilized ^{67}Ga as an agent for total body labeling Additional isotopic materials or agents with different photon emission spectra which selectively localize in lung liver bone and spleen are then injected as a second isotopic label which permits the activity and contribution to the image of the lung liver bone or spleen to be subtracted This leaves as a residual image the abnormal isotope accumulation in e g neoplastic or inflammatory tissue This method was applied to the evaluation of selected patients with Hodgkin s disease and non Hodgkin s

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mphoma in this clinic The present report describes preliminary experiences with is method The histologic appearances were correlated with capability for detection he purpose of this comparison was to determine whether the reduction of the normal background enhanced the ability to recognize ^{6} Ga true scan abnormalities

Materials and Methods

The material consisted of 38 patients 24 with Hodgkin s disease and 14 with on Hodgkin s lymphoma All patients had standard evaluation carried out at this niversity including history physical examination complete blood count p a and teral chest films and tomography of hilar regions as indicated lymphangiography EE 1969) liver function tests liver and spleen scans (MILDER et coll 1975) and rography In all cases of Hodgkin s disease laparotomy staging was done (KAPLAN 972) which included splenectomy multiple lymph node biopsies needle and wedge ver biopsies and bone marrow biopsy Bone scan or bone radiography were used lectively In more recent experience with non Hodgkin s lymphomas laparotomy taging has been used very selectively (JONES et coll 1972) All patients were clinically aged according to Ann Arbor staging system (see KAPLAN)

Ga citrate was obtained as a sterile pyrogen free commercial product A dose of 5 μCi/kg (2-3 mCi) was administered intravenously ^{67}Ga decays with a $T_{\frac{1}{2}}$ of 78 ours The scanning procedure was usually performed at approximately 48 to 72 ours after intravenous administration of the nuclide occasionally scanning was elayed only 30 hours Standard imaging instruments were used for photoscanning ne ^{6} Ga was performed first Then the second labeled agent was injected and scanned ogether with the ^{6} Ga

^{99}Tc^{m} bone seeking agents (e g Diphosphonate) ^{99}Tc^{m} sulfur colloid and ^{99}Tc^{m} abeled human albumin microspheres were used as bone liver and spleen and lung canning agents respectively These imaging agents were prepared and injected at ppropriate intervals before the scanning procedure The two scans were then dis layed as described in the following

A dual 12 7 cm total body rectilinear scanner with dual pulse height analyzers nd subtraction feature was utilized A high energy 19 hole broad focus collimator with 10 cm focal distance was used to collimate the ^{67}Ga gamma ray energies as well s those from ^{99}Tc^{m} A medium energy medium focus collimator with a 15 3 cm focal distance was also used to collimate both ^{67}Ga and ^{99}Tc^{m} gamma energies The photoscans were displayed without minification on 35 cm × 43 cm Kodak safety RP film with a 2 mm line spacing and information density of 500

All signal pulses corresponding to ^{6} Ga and ^{99}Tc^{m} gamma interactions from the detectors were directed to each position of two pulse height analyzers One pulse height analyzer by use of energy selection permitted the ^{67} Ga 184 and 300 keV photo peak counts to be recorded on the photoscan The resulting photoscan therefore demonstrates the distribution of Ga The other pulse height analyzer was cali

Table 1

Results of ⁶ Ga scans in cases of Hodgkin s disease

Classification	No of patients	Correlation of positive ⁶⁷Ga scan in major* involvement sites
Nodular	11	10
Mixed cell	5	4
Lymphocyte predominance	4	3
Recurrent disease	4	3
Total	24	20 (83)

* Clinically positive obvious disease by examination radiography or laparotomy (true positive)

brated to encompass counts of the 140 keV peak of $^{99}Tc^{m}$ Each of these pulse height analyzers was normalized to 100 per cent over the area of greatest activity over the liver A subtraction photoscan was produced by subtracting the output of one pulse-height analyzer from the other The subtraction scan and the ⁶ Ga photoscan were then produced separately and simultaneously An average information density of 400 counts/cm was maintained on all same The 90 degree Compton scatter occurs at about 135 keV and no doubt contributes some background (~5°) to that detected by the second pulse height detector Presently higher counts are being used Similarly it has become evident that a scintillation camera or Phocon scanning with computer data storage and subtraction is also easily performed with still better demonstration

Current laparotomy staging methods were used for all patients with Hodgkin s disease (see KAPLAN) and ensured a complete evaluation of the disease for comparison with the accuracy of ^{67}Ga scanning For the non Hodgkin s lymphoma laparotomy staging was not routinely performed and therefore radiographic localization was more important Independent histologic review of all lymphomas was carried out by the Southeastern Cancer Group (SEG) pathology reviewers The scan was correlated with the clinical localization of the gross distribution of the disease That is the major comparison was limited to true positive cases only since it has already been shown that detection of inapparent disease by ⁶ Ga is not accurate and many false negatives occur (ADLER 1975 GREENLAW et coll HORN et coll 1976 JOHNSTON et coll MCCAFFREY et coll 1976)

In the data to be presented all cases were patients with documented Hodgkin s or non Hodgkin s lymphoma Correlation was directed to sites of obvious involvement or abnormality by one or other means of evaluation including physical examination biopsy radiography laparotomy or similar means

No effort was made for a site by site correlative comparison unless a palpable radiographic or biopsy proven obvious major abnormality was apparent It has already been established that microscopic disease and non obvious disease has a high

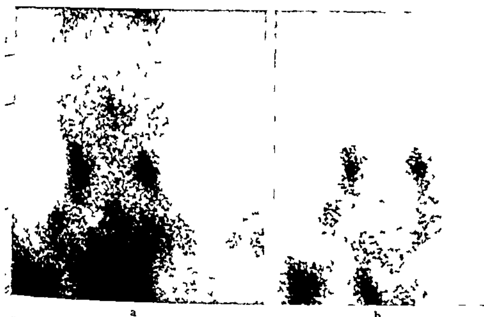


Fig. 1 a) ⁶⁷Ga scan of neck and chest b) ⁶⁷Ga subtraction scan ⁹⁹Tcᵐ removed bone activity from the Ga scan.

frequency of false negatives and moreover is often below the detection sensitivity of the ⁶⁷Ga method Thus the evaluation concentrated on the capability of the subtraction method to recognize obviously diseased sites

Results

Correlation was found in localization of Hodgkin s disease in patients with proven disease as has been shown by ADLER GREENLAW HORN et coll JOHNSTON et coll McCAFFREY et coll Patients in the present serie were distributed through all stages of disease including 4/20 who were recurrent 20/24 (83 %) had evidence of accumulation in major diseased sites (Table 1) and this experience is compatible with the report by JOHNSTON et coll A high percentage of the grossly involved clinically apparent sites showed ⁶⁷Ga uptake especially for Hodgkin s disease All histologic types accumulated activity well and in all patients the accumulation of definite abnormal activity indicated an abnormality In the neck chest, axilla (Fig 1) and groin regions the ⁶⁷Ga method correlated well with gross disease involvement as assessed by clinical examination or radiography with or without subtraction In the abdomen the subtraction scanning reduced the bone liver and spleen backgrounds (Figs 2 3) But the abdomen and the pelvis contain bowel activity which made the evaluation of the images difficult The pelvis also has activity in the bladder which can be subtracted but subtraction of bone and bladder made detection of small

Table 2

Results of ⁶⁷Ga scanning in cases of non Hodgkin s lymphoma

Classification	No of patients	Correlation of positive ⁶⁷Ga scan in major involvement sites*
Well-differentiated	6	4
Moderately to poorly differentiated	4	3
Histiocytic lymphoma	1	1
Unclassified lymphoma	3	0
Total	14	8 (57)

Obvious clinical disease by examination radiography or laparotomy (true positive)

residual masses difficult unless located in the groin or external iliac node cha[in] Meticulous bowel preparation greatly reduced bowel background but this remain[ed] a problem due to the background activity contributed ⁶⁷Ga made it possibl[e] to detect axillary supraclavicular hilar mediastinal para aortic retroperitoneal ili[ac] and groin disease (Figs 2 3) The negative case included one patient with Stage IA disease who had a single involved node excised (cervical) and was ne ative ? had prior irradiation with response and tumor disappearance one had recurrent d se [in] bone marrow and was negative (Table 1) No false negatives were observed After completion of radiation therapy ⁶⁷Ga localization was negative if response was complete

The observations showed a diagnostic accuracy of 57 per cert (Table 2) for non Hodgkin s lymphoma In all forms of non Hodgkin s lymphoma involved sites were localized except in the unclassified lymphoma This included both lymphocytic and histiocytic types and raises the question of the accuracy of tumors placed in the category of unclassified lymphoma Non Hodgkin s lymphoma constitutes a much more capricious disease with a much less orderly distribution and more extranodal involvement as well as microscopic spread Nonetheless the disease was detected in nearly all sites including orbit bone and nodes of the cervical axillary mediastin[al] mesenteric parotid and retroperitoneal regions Although the disease was excellently localized in some patients (Figs 1–3) false negatives in the neck abdominal peri aortic and iliac regions were observed The negative scans were as follows 3 were considered unclassified lymphoma 2 well differentiated lymphoma (abdominal nodes) one iliac node and bone marrow involvement (moderately to poorly differentiated)

A single case with histiocytic lymphoma was positive which has been found for this type of tumor At the present level of development abdominal examination was not greatly improved over standard ⁶⁷Ga scanning although background was greatly reduced Some difficulty in evaluation of the cervical and hilar region was encountered and did not correlate with physical examination surgical or radiographic findings

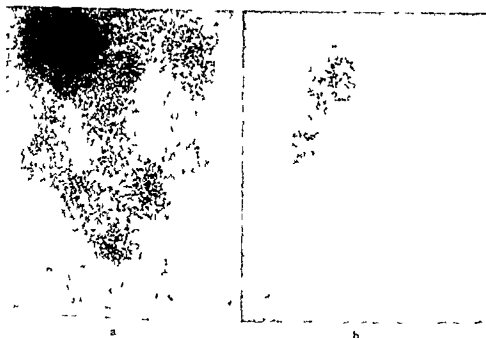


Fig. 2. a) ^{67}Ga scan of abdomen b) ^{67}Ga subtraction scan Uptake in liver spleen bone and urogenital tract subtracted by ^{99}Tc^{m} labeled compound In (b) uptake in retroperitoneal lymphoma not visible in (a) due to superimposition of hepatic uptake

Discussion

The purpose was to determine the feasibility of the ^{67}Ga multiple subtraction method in Hodgkin s disease and non Hodgkin s lymphoma and to correlate the histologic findings and clinical evaluation with the scanning results The Ann Arbor meeting (see KAPLAN) proposed a staging scheme and suggested that the use of isotope methods such as ^{67}Ga may be a promising procedure for clinical diagnostic evaluation of patients with Hodgkin s disease and lymphoma (Ann Arbor Conference) JOHNSTON et coll and GREENLAW et coll reported a 50 to 88 per cent accuracy by positive accumulation of activity in diseased areas However the frequency of equivocal scans has limited the evaluation of data obtained by the ^{67}Ga scanning method Considerable activity also accumulates in normal liver spleen bone and bowel and greatly interferes with the evaluation of abnormalities in sites such as the head mediastinum abdomen para aortic regions and pelvis (ADLER EDWARDS & HAYS 1969 1970 HIGASHI et coll 1972 MCCAFFREY et coll LAVENDER et coll 1971 LEVY et coll 1975) In the present experience concentration of ^{67}Ga was found in patients with Hodgkin s disease and the various types of lymphoma and the results of GREENLAW et coll and JOHNSTON et coll were confirmed A correlation of ^{67}Ga cervical scans with histologic subtypes was found True positive correlations were



Fig 3 a) ^{67}Ga scan Uptake in mid abdomen in para aortic lymph nodes and tumor b) ^{67}Ga subtraction scan The tumor uptake is more evident after removal of uptake in liver bone and uro-genital tract

comparable with those of previous reports being 83 per cent (Table I) for Hodgkin s disease

Non Hodgkin s lymphoma was also detected by ^{67}Ga or the ^{67}Ga subtraction scanning method and 57 per cent of the cases had uptake in major involved sites. In Hodgkin s disease the sites are usually massively involved and the lymphoid regions of the body are almost invariably involved For non Hodgkin s lymphoma negative scans appeared to correlate with the smaller lesions although low or poor uptake of isotope and perhaps errors in evaluation of pathology (undifferentiated tumors) contributed

This investigation has focused on detection of obvious disease and the possible contribution of subtraction scanning to detection of abnormalities Clearly by reduction of background detection of abnormalities was facilitated However at the present state of development limitations were obvious The positive scans correlated well with sites of obvious clinical disease (true positive by examination, radiography or laparotomy) Although background was reduced by subtraction scanning further refinement of instrumentation greater purity of organ specific radiopharmaceuticals higher specific activity of ^{67}Ga and greater versatility in optimizing differential enhancement of the image appears to be necessary The preliminary results were comparable with present ^{67}Ga scanning but further improvement is necessary before reduced equivocal scans and improved and accurate tumor detection and localization is possible with this method One of the important problems is the need for determination of a size threshold for lesion detection as background is reduced

^{67}Ga scanning is a procedure which is potentially useful for (1) pretreatment evaluation and determination of the extent of disease (2) posttreatment follow up and (3) detection of recurrence The multiple isotope subtraction scanning method may permit a more accurate diagnosis of abnormal sites by reducing background

ise The method can be applied in principle to any imaging system for reduction backeround noise

A better understanding of the radiopharmaceuticals and their metabolism is needed ie cause of increased gallium concentration in tumors and inflammatory tissue is iknown and must be further investigated with animal tumor models and human sue (SWARTZENDRUBER et coll 1971)

SUMMARY

Recently a new method was described the ⁶ Ga subtraction scanning method Ga cumulates in neoplastic and inflammatory tissue The subtraction method was applied r e 'uating 38 patients with Hodgkin s disease and non Hodgkin s lymphoma The eliminary experiences are described It was found that the diagnostic accuracy is com irab' to that of ⁶ Ga scanning The subtraction method offers potential improvement of e accuracy for equivocal scans but further technological refinement is needed before the ethod can be widely applicable

ZUSAMMENFASSUNG

Die neue Methode ⁶ Ga Subtraktions Scanning wurde zur Auswertung von 38 Patienten it Hodgkinscher Krankheit und nicht Hodgkinschem Lymphom verwendet Die Methode is e si h darauf dass ⁶⁷Ga sich in neoplastischen und inflammatorischen Geweben an ichert Die vorlaufigen Erfahrungen deuten darauf hin dass die diagnostische Genauig it vergleichbar mit der von ⁶⁷Ga Scanning ist Die Subtraktionsmethode ermoglicht eine erbesserung der Genauigkeit bei unsicheren Scans es ist jedoch eine weitere technologische erfeinerung notwendig bevor die Methode in weitem Umfang verwendet werden kann

RESUMÉ

La nouvelle methode de scintigraphie par le Ga avec soustraction a ete utilisée pour xaminer 38 malades atteints de maladie de Hodgkin et de lymphome non Hodgkinien Elle base sur le fait que ⁶ Ga s accumule dans les tissus neoplastiques et inflammatoires Les xperiences preliminaires indiquent que l exactitude du diagnostic est comparable a celle e la sc n igraphie par le Ga La methode de soustraction fournit une amelioration poten elle de l exactitude pour les scintigraphies douteuses mais des perfectionnements techno- ogiques sont necessaires avant que cette methode soit largement applicable

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MEDULLOBLASTOMA

Treatment results

BODIL NUCHEL and A P ANDERSEN

Brain tumour is the second most frequent type of malignant disease in children only superceded by leukemia In children under 15 years of age medulloblastomas constitute ca 20 per cent of intracranial tumours (BAILEY et coll 1939 BLOOM et coll 1975 CRAIG et coll 1949 MACKAY et coll 1968) The disease is more common in boys than in girls with a ratio of 2-4 1 (BLOOM et coll 1969 SMITH et coll 1973)

The medulloblastoma originates from the cerebellum and 4th ventricle and frequently infiltrates the subarachnoidal space with a tendency to spread via the cerebrospinal fluid resulting in metastases along the cerebrospinal axis

Surgery alone is not enough to control the disease and as the medulloblastoma usually is sensitive to radiation supervoltage irradiation of the whole cerebrospinal axis is indicated in all cases The present surgical policy is to restrict the operation to reduce the surgical mortality and the risk of neurologic disability but to obtain satisfactory CSF flow and tissue for microscopy The irradiation must start as soon as possible after the operation

Material

The material comprised 44 patients treated at the Radium Centre during the period between January 1 1963 and December 31 1975 The preceding surgical procedure was carried out in the neurosurgical departments and the histologic examination in the neuropathologic department of the Aarhus Municipal Hospital

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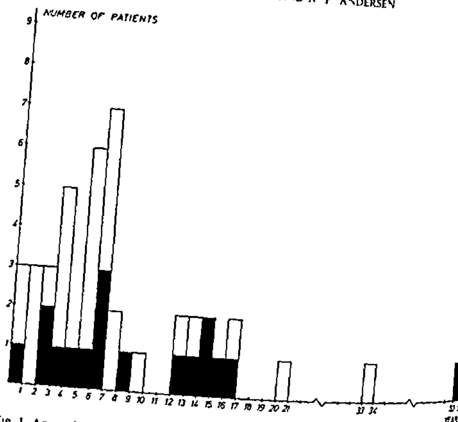


Fig 1 Age and sex distribution

The series includes all patients referred to the Radium Centre and the follow up is complete with an observation time of 1 to 13 years

The age and sex distribution appears in Fig 1 Eighty six per cent of the patients were children under 15 years of age which agreed with the report by Bloom et coll (1969) and with the higher frequency in the first decade The average age for children was 6 years and the male/female ratio for children was 1 7 1 and for the entire material 1 6 1

Symptoms The initial symptoms are given in Table 1 Vomiting and headache were the most dominating symptoms Eighty two per cent of the patients had a history under 6 months and 59 per cent under 3 months the longest being 24 months (Table 2)

Tumour localisation All the tumours were located in the 4th ventricle except one which was located in the roof of the 3rd ventricle and one which was located in the brain stem According to the operation findings 7 patients had seeding to the surface of the cerebellum 4 invasion of the brain stem and 3 invasion of the upper part of the spinal canal

Table 1

Initial symptoms and signs

Symptoms	Per cent
Vomiting	86
Headache	75
Dissiness, ataxia	61
Visual disorder	36
Mental changes	32

Treatment The primary treatment was surgery The tumours appeared to be moved in 13 patients in 22 patients a partial resection was carried out and in 8 atients only biopsy

In one case no microscopic diagnosis was obtained as the tumour was located in ie brain stem but clinically the case was assessed as a medulloblastoma

In the first 9 years of the period high voltage irradiation of the whole skull by pposing lateral fields was given with an intended dose of 45Gy/6 weeks followed y irradiation of the spine to the second sacral segment with an intended dose of 0Gy/4 to 5 weeks

In the last 4 years of the period a technique introduced by CHANG et coll (1969) as used i e a tumour dose of 35Gy/3½ to 4 weeks to the entire skull and 35Gy/5 eeks to the spine and finally an additional dose of 15Gy/2 weeks to the posterior ssa

However it was found necessary in several cases to diverge from this principle for rious reasons Especially the spine had to be irradiated over a longer period sually because of bone marrow depression with leukopenia In 10 patients the spine as not irradiated as their general condition was considered too poor

One of these had a blast relapse of an acute lymphatic leukemia One patient ceived irradiation of the spine 7 years after the primary treatment because sub-achnoid metastases had been detected One patient was not irradiated as the parents

Table 2

Duration of history

Duration (months)	No of cases	Per cent
1	7	16
1	19	43
3–5	10	23
6–1	5	11
1	3	7
Total	44	100

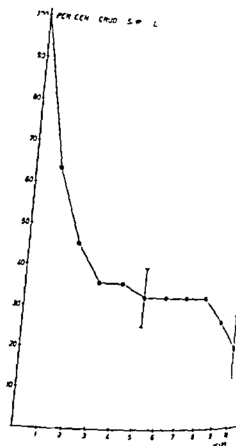


Fig 2. Cumulative *crude* survival (actuarial method)—all patients

refused permission *In 4 cases* the irradiation was discontinued before the intended dose level was *reached* because of deteriorating condition of the patients A shunt operation was *performed in* 16 patients before or immediately after the irradiation because of *increasing intracranial* pressure

Results

The results of *treatment* for all patients (adults and children) and for children separately are *given in Fig* 2 and Table 3 The 3 *year* and 5 year survival for all patients was 36 *per cent and 33* per cent respectively This confirms well the results of BOUCHARD (1966) *who* found a 3 year survival of 36 per cent In a smaller series CHANG et coll found *a* 3 year survival *for adults and children of* 60 per cent (6/10) and PATERSON & FARR *(1953)* of 65 per cent (11/17) The 3 year and 5 year survival for children in the *present* series are 37 and 33 per cent respectively BLOOM et coll (1975) and *McFARLAND et coll* (1969) found a 3 year survival for children of [illegible] per cent and BOUCHARD 33 per cent Better results have been reached in smaller series PATERSON & FARR 54 per cent (7/12) *CHANG et coll* 55 *per cent* (5/9) [illegible]

Table 3

Cumulative survival rate in per cent (Standard error by Greenwood's approximation)

Years after treatment	All patients	Children	Boys	Girls
1	64±7	61±8	63±10	57±13
3	36±7	37±8	37±10	36±13
5	33±7	33±8	37±10	29±12
10	20±8	22±10	—	19±11

HELINE (1975) 88 per cent (7/8) VESTERGAARD & JOHANSEN (1974) found a 5-year survival of 22 per cent A less favourable prognosis for boys than for girls was found by BLOOM et coll (1969) which however was not confirmed in the present series (Table 3)

Of the 13 surviving patients 8 are in good condition (62%) although 5 have slight neurologic symptoms and signs while 3 are completely normal 2 (15%) are intellectually or neurologically reduced but capable of self-care and 3 (23%) have severe psychiatric and neurologic symptoms and signs and are incapable of self-care Autopsy was performed in 15 of the 31 patients who had died Local recurrence alone was found in 2 cases while 11 in addition had metastases to the cerebrum brain stem or the spinal cord One patient had emollition possibly radiation necrosis while only one patient was recurrence free but died from hydrocephalus caused by adhesions

Discussion

Surgery alone cannot cure medulloblastoma The present policy is to remove as much tissue as possible partly for microscopic diagnosis and partly to secure sufficient CSF flow if necessary via a shunt By more extensive operation the mortality and the risk of serious neurologic symptoms and signs are increased Therefore post operative irradiation is indicated The irradiation should include the primary tumour area in the posterior fossa as well as the rest of the cerebrospinal axis to prevent seeding of tumour cells Most authors (BLOOM & WALSH 1975 CHANG et coll) recommend a dose of 50 to 55 Gy/7 to 8 weeks to the fossa posterior and a prophylactic dose of the rest of the neuroaxis of 30 to 35 Gy in 5 weeks

BROWN et coll (1977) state that as long as no sign of spinal involvement exists a dose of 25 Gy to the spine is sufficient thus reducing the risk for retardation of the spinal growth The possible occurrence of this complication is not analysed in the present series

A few of the present patients did not receive adequate irradiation after the current standards The results of 33 per cent 5 year survival correspond well to those in larger materials but it is possible that they could have been better if all patients had chosen

to go through with the treatment Other authors (LAMPE & MACINTIRE 1954 BLOOM & WALSH BROWN et coll 1977) state that most recurrences occur within 3 years following the treatment and that patients who survive 3 years without sign of recurrence have a good chance of being long term survivors The present results seem to confirm this opinion

The clinical value of chemotherapy in medulloblastoma is not yet clear but responses have been reported in many cases with the use of intrathecal methotrexate and with BCNU CCNU and vincristine (SHAPIRO 1975) BLOOM (1975) has supplemented the usual medulloblastoma treatment with intravenous vincristine oral CCNU and intrathecal methotrexate in a preliminary investigation The results are not conclusive, but sufficiently encouraging to suggest a prospective controlled investigation

SUMMARY

A series of 44 patients with medulloblastoma is presented The treatment was primary operation followed by irradiation of the entire CNS The 3 year and 5 year survival rates for children and adults together were 36 and 33 per cent respectively and for children alone 37 and 33 per cent respectively No certain difference in the prognosis for boys and girls was found

ZUSAMMENFASSUNG

Vierundvierzig Patienten mit Medulloblastom werden beschrieben Die Behandlung war Operation mit nachfolgender Bestrahlung des gesamten zentralen Nervensystems Die 3 Jahre und 5 Jahre Überlebensrate fur Kinder und Erwachsene zusammen betrug 36 bzw 33 Prozent und fur Kinder allein 37 bzw 33 Prozent Keine sichere Differenz in der Prognose fur Jungen und Madchen wurde gefunden

RESUMÉ

Présentation d une série de 44 malades atteints de médulloblastome Le traitement a consisté en une opération suivie d irradiation de tout le système nerveux central Les taux de survie à 3 ans et à 5 ans pour les enfants et les adultes comptes ensemble ont été respectivement de 36 et 33 pour cent et pour les enfants comptés seule respectivement de 37 et 33 pour-cent Les auteurs n ont pas trouvé de différence certaine dans le pronostic pour les garçons et pour les filles

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BILE SALT MALABSORPTION IN THE RADIATION SYNDROME

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Intestinal reactions to radiation therapy of pelvic malignancies are a well known complication (CALAME & WALLACH 1967 SMITH et coll 1968 WEGHAUPT 1968 DECOSSE et coll 1969 WELLWOOD & JACKSON 1973 DONALDSON et coll 1975) Acute intestinal reactions are common whereas chronic injury of the intestine is encountered more seldom An increase in the radiation dose has improved the survival rate in pelvic malignancies but also increased the risk of intestinal injury The pathology and surgical management of gross intestinal injury has been described by several authors e g LINDAHL (1970) DENCKER et coll (1971) JOELSSON & RA (1973) DEVENEY et coll (1976) In these series the frequency of severe small intestinal injury although varying seems to be low but minor or subclinical injury may be more frequent

Diarrhoea is a prominent symptom in both acute and chronic radiation enteritis Several factors may be involved in the pathogenesis such as radiation induced abnormalities in the colonic mucosa fat malabsorption or changes in intestinal bacterial flora

However excessive amounts or bile salts in the colon as a result of ileal dysfunction—so-called cholerheic enteropathy (HOFMANN 1967)—are a well known cause

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f diarrhoea after ileal resection NEWMAN et coll (1973) found evidence of an in reased deconjugation of bile salts in women after pelvic radiation therapy and in ost cases a permanent alteration of bowel habits with diarrhoea was noted It was fore considered motivated to investigate whether bile salt malabsorption is resent in patients with gastrointestinal symptoms after pelvic irradiation

Material and Methods

The material consisted of 20 women (age 42–76 years mean 61 years) previously rradiated for malignant gynaecologic tumour (Table) The patients were admitted o this hospital because of gastrointestinal complaints The control material com rised 11 patients with diarrhoea and normal ileum (as found at radiography examina ion or operation) 5 with ulcerative colitis and 6 with acute gastroenteritis During a cal collection the patients except those with acute gastroenteritis were kept on a tandard hospital diet containing about 80 gram of fat Stools were analysed for fat y the method of VAN DE KAMER et coll (1949)

Bile salt malabsorption was measured as the faecal bile salt (FBS) excretion of an travenous dose of labelled bile acid as described by ANDERSSON (1976) After an vernight fast 10 μCi of carboxyl ^{14}C-cholic acid (NEC 241 New England Nuclear pecific activity 44 5 mCi/mmol radiochemical purity greater than 99 %) was slowly jected into the tubing of an intravenous saline infusion After 24 hours the subject was given an oral dose of carmine red (0 6 g) as a faecal marker Stools were col ected from the time of injection until a carmine coloured specimen appeared The ollect d stools were combined and homogenized and samples of about 0 25 g precision 0 0001 g) each were analysed in triplicate for ^{14}C activity by liquid scintil ation technique (Tri Carb Packard model 3320) after digestion with Protosol The tivity in the total faecal collection was calculated as a percentage of the activity n ed This figure expresses the fraction of the bile acids which is lost in faeces during 24 hours of enterohepatic circulation

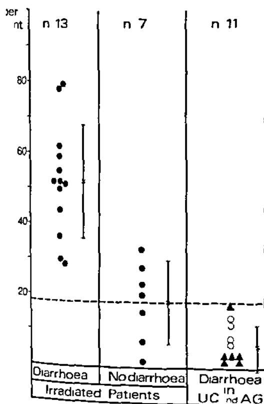
The mean recovery of 6 25 μCi carboxyl ^{14}C cholic acid added to faeces wa found o be 99 per cent (SD 4 7) in 24 determinations in patients with ileal disease (AN ERSSON 1976) The mean recovery in faeces of the injected dose has been found to be 100 per cent (SD 8 5 %) in 18 determinations when stools were analysed until they were free of activity (up to one week after injection) As a consequence measurements of ^{14}C activity in urine have not been found necessary The reproducibility of the method has been tested in 9 patients by repeated examinations 3 to 10 months later No statistically significant difference was found (Wilcoxon matched pairs test)

The normal range of this test is based on determinations in 16 patients with colo rectal disorders without diarrhoea who were considered to have completely normal small bowel function (FILIPSSON 1977) These patients had a mean FBS excretion of 5 8 per cent (SD 3 9) The upper normal limit is thus arbitrarily set at 18 per cent (mean + 3 SD)

Table

Age tumour location irradiation data time after irradiation symptoms faecal bile salt (FBS) and faecal fat in 20 patients previously irradiated Lin denotes radiation delivered by roentgen linear accelerator Cobalt use of ⁶⁰Co Mobaltron Ra intracavitary radium therapy

Case No location of carcinoma	Age (years)	Radiation source	Dose (Gy)	Time after radiation <3 mths	3 mths–2 yrs	>2 yrs	Symptoms (D = diarrhoea A = abdominal pain, M = malabsorption, R = rectal haemorrhage)	FBS (per cent)	Faecal fat (g 4 h)
Patients with diarrhoea									
Uterine body									
1	56	Ra + Lin acc	30	−			D A	79	2.4
2	75	Ra − Cobalt	30	−			D	67	8.4
3	72	Ra + Lin acc	30			−	D	51	7.6
4	76	Ra + Lin acc	20	+			D A, R	44	3.9
Uterine cervix									
5	63	Ra + Cobalt	40		−		D A, M	78	12.2
6	53	Ra + Lin acc	40		−		D	59	.0
7	73	Ra − conventional rtg 2 000 R skin dose				+	D A, M	57	16.0
8	55	Ra + 3 Lin acc	40			+	D	30	2.7
9	55	Ra + Lin acc	28			+	D A	79	3.6
Ovary									
10	55	Cobalt	40	+			D A	55	1.6
11	62	Ra + Lin acc	40		−		D M	57	17.0
12	66	Ra + Lin. acc	40	−			D M	50	17.9
13	48	Lin acc	60			+	D M	37	18.2
Patients without diarrhoea									
Uterine body									
14	56	Ra + Betatron	43			+	R	20	1.9
Uterine cervix									
15	62	Ra + Lin acc	42		+		R	33	2.6
16	57	Ra + Lin acc.	30			+	A	28	4.5
17	52	Ra − Lin acc.	40	+			A	23	4.8
18	71	Ra + Lin acc	40			+	R	7	6.7
19	41	Ra − Cobalt	62		+		A R	1	5.4
Ovary									
20	71	Conventional rtg	42			+	A R	15	5.4



Faecal bile salt excretion (in per cent) in 20 irradiated patients and in 11 control patients with ulcerative colitis (U C) and acute gastroenteriti (A G) Bars indicate mean ± SD Upper normal limit is indicated by dotted line

Results

Of the 20 irradiated patients 17 had an increased FBS excretion (Figure) All patients with diarrhoea had an increased FBS excretion 52±16 % (mean ± SD) The patients without diarrhoea had an FBS excretion of 18±12 % (mean ± SD) The group difference is significant (p < 0 001 Student s t test) The control patients with diarrhoea had an FBS excretion of 5 7±6 2 % (mean ± SD)

The faecal fat content of the irradiated patients with diarrhoea was 9 1±6 4 g per 24 h (mean ± SD) The patients without diarrhoea had a faecal fat output of 4 6±1 8 g per 24 h The difference is not significant (Student s t test) No correlation between FBS excretion and faecal fat output (linear regression analysis) was found

Discussion

In the distal part of the ileum a specific absorption of bile salts takes place (BORGSTRÖM et coll 1963) Ileal dysfunction will cause malabsorption of bile salts and concomitant cholerheic diarrhoea (HOFMANN)

Experiments indicate that radiation will impair bile salt absorption in rats (SULLIVAN 1965) and that bile salts play a role in the pathogenesis of diarrhoea after ir

radiation in the laboratory animal (JACKSON & ENTENMAN 1959 SULLIVAN 1967) In external irradiation of the pelvis varying length of the distal small intestine is frequently located within the field of treatment (GREEN et coll 1975) As the small bowel is sensitive to radiation ileal injury could be expected after pelvic irradiation. NEWMAN et coll found abnormal cholyl glycine 1 ^{14}C breath tests indicating increased deconjugation of bile salts in 16 of 17 randomly selected women after pelvic irradiation The authors state that the breath test does not distinguish between stagnant loops or ileal injury but they are of the opinion that one or both of these mechanisms must be involved to explain their findings

In the present series all irradiated patients with diarrhoea had bile salt malabsorption indicating ileal dysfunction The fact that only 7 of 20 patients had signs of fat malabsorption is in accordance with previous observations that FBS excretion is a more sensitive test of ileal function than is the determination of faecal fat excretion (FROMM et coll 1973 FILIPSSON) The increased FBS excretion of irradiated patients with diarrhoea compared to those without is indirect evidence that bile salt malabsorption is an important factor in the pathogenesis of diarrhoea after pelvic irradiation Diarrhoea per se however is not accompanied by an increased FBS excretion as evidenced in the patients with ulcerative colitis and acute gastroenteritis

As a low fat diet regimen (BOOTH et coll 1964 ANDERSSON 1974) and bile sequestering agents (HOFMANN & POLEY 1969) have been shown to be effective in the treatment of cholerheic enteropathy in Crohn s disease these treatments may be used to alleviate symptoms in the radiation syndrome A therapeutic trial of low fat diet treatment of these patients is in progress The results thus far are promising

SUMMARY

The fraction of faecal activity (FBS) excreted after intravenous administration of ^{14}C labelled cholic acid was measured in 20 patients with gastrointestinal symptoms (diarrhoea, abdominal pains malabsorption and rectal haemorrhage) after pelvic irradiation An FBS excretion of 52 ± 16 per cent (mean $\pm$ SD) was found in 13 patients with diarrhoea and 18 ± 12 per cent in 7 patients without diarrhoea In normals the excretion is not above 18 per cent Bile salt malabsorption appears to be an important factor in the pathogenesis of diarrhoea in these patients

ZUSAMMENFASSUNG

Der Anteil der fakalen Aktivitat der nach intravenoser Verabreichung von ^{14}C gezeichneter Cholsaure ausgeschieden wurde wurde bei 20 Patienten mit gastrointestinalen Symptomen (Diarrhoe abdominale Schmerzen Malabsorption und rektale Blutung) nach Beckenbestrahlung untersucht Eine fakale Aktivitat von 52 ± 16 Prozent (Mittel $\pm$ SA) wurde bei 13 Patienten mit Diarrhoe gefunden und 18 ± 12 Prozent bei 7 Patienten ohne Diarrhoe. Bei gesunden Personen ubersteigt die fakale Aktivitat nicht 18 Prozent Gallensalz Malabsorption scheint ein bedeutungsvoller Faktor bei der Pathogenese der Diarrhoe dieser Patienten zu sein

RESUME

La fraction de l activite fecale excrétée après administration intraveineuse d acide cholique marque au ^{14}C a eté mesuree chez 20 malades ayant des symptomes gastro intestinaux (diarrhee douleurs abdominales malabsorption et hémorragie rectale) apres irradiation pelvienne Une excretion de l activité de 52 ± 16 pour-cent (moyenne ± DS) a ete trouvee chez 13 malades ayant une diarrhee et 18 ± 12 pour-cent chez 7 malades sans diarrhee Dans les cas normaux l excretion ne depasse pas 18 pour-cent La malabsorption des sels biliaires parait etre un facteur important de la pathogénie de la diarrhée chez ces malades

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FROM THE DEPARTMENTS OF TISSUE CULTURE AND BIOPHYSICS NORSK HYDRO'S INSTITUTE FOR CANCER RESEARCH THE NORWEGIAN RADIUM HOSPITAL MONTEBELLO OSLO NORWAY

EFFECTS OF DIFFERENT GROWTH CONDITIONS ON SURVIVAL AFTER IRRADIATION IN HYPOXIA OF HUMAN CELLS (NHIK 3025) IN VITRO

ERIK O PETTERSEN and TORE LINDMO

The effect of roentgen irradiation under extremely hypoxic conditions on the colony forming ability of cells of the human line NHIK 3025 has previously been investigated on asynchronously growing populations (PETTERSEN et coll 1973 1974 a b 1976) The survival curves were found to fit well to two exponential lines Such a curve shape is unusual for mammalian cells and the data should be considered on the basis of two main sources for variation in inactivation kinetics of asynchronously growing cells

1) Asynchronously growing populations of cells are generally heterogeneous with respect to sensitivity to radiation due to a variation in sensitivity throughout the cell cycle (see SINCLAIR 1968 for a review) The survival curves of asynchronously growing populations are therefore a resultant of the different survival curves for cells in various stages of the cell cycle

2) Populations which have been exposed to some inhibition of their growth show radiation response different from that of exponentially growing populations apart from what is caused by differences in cell cycle distribution (HAHN 1968 BERRY et coll 1970) A population which is kept in plateau phase before it is used in experiments may therefore have a radiation response different from that of a population kept in continuous exponential growth by frequent reculturing Another

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example of this type of variation in sensitivity is the transient fluctuations in survival level observed after irradiation at various times during the first 10 to 20 hours after trypsinization (ELKIND et coll 1961 PHILLIPS & TOLMACH 1965)

As to the asynchronously growing populations previously reported (PETTERSEN et coll 1973 1974 a b 1976) only cells from 1 2 and 3 day old cultures were used for experiments These populations were recultured every 7th day and the medium was changed on the 3rd and 5th day Populations used in experiments were supposed to be in the log phase of growth which will be confirmed by the present results

In recent reports (PETTERSEN et coll 1977 a b) data on the sensitivity of NHIK 3025 cells in different stages of the cell cycle have been reported These investigations were done on cells synchronized by the method of mitotic selection Mitotic cells were selected from populations which had been kept in exponential growth by frequent reculturing over several weeks and therefore may be suggested to comply with the concept of balanced growth as proposed by ANDERSON et coll (19.. The concept is based on the definition of an unbalanced state for single cells An unbalanced state is one in which the cell has a composition not shown by any cell in the course of the normal life cycle By normal life cycle is meant a cell cycle which under constant growth conditions is repeated several times (e g indefinitely) with no changes

The survival curves of the synchronized populations of NHIK 3025 cells were found to be different in shape from that previously published for asynchronously growing populations especially at low radiation doses (PETTERSEN et coll 1974 a 1977 a) This finding initiated the present experiments which include determination of growth (increase in cell number) for NHIK 3025 cells recultured as were those in previous work (named weekly recultured populations in the present report) Survival curves for cells from such populations which are recultured every 7th day and irradiated at different times after reculturing are compared with survival curves for cells from frequently recultured populations In addition survival curves for synchronized populations of cells irradiated in G1 S G2 and mitoses are given

The data indicate that cells from the weekly recultured populations in log phase may be less well-defined than formerly believed Both cell cycle kinetics and radiation response of such cells were different from what was found for frequently recultured populations

Material and Methods

Two types of asynchronously growing populations of NHIK 3025 cells were used

Weekly recultured populations These were trypsinized and recultured once a week and the medium was changed after 3 and 5 days (or 2 and 4 days) (PETTERSEN et coll 1973) The pH varied between about 7 6 and 6 9 The sensitivity to radiation was recorded both during log and plateau phase

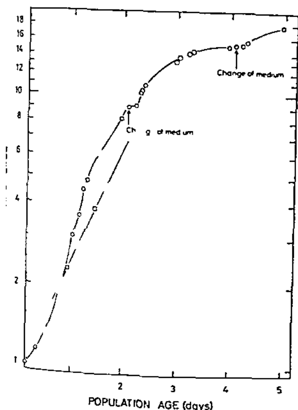


Fig 1 Growth measured as increase in cell number for NHIK 3025-cells as a function of time after reculturing for a weekly recultured population (○) and a frequently recultured population (□) The ordinate axis is logarithmic The measurements were performed by repeated counting of the cell number within delineated areas of the culture flasks An inverted microscope with phase contrast optics was used and the whole procedure took place in an incubator room at 37 C

Frequently recultured populations These were tried kept in continuous exponential rowth and were always recultured every 2nd or 3rd day before the monolayer ecame confluent There was no significant variation in pH of the medium (pH = 7 2)

Synchronized populations of cells were produced from the frequently recultured opulations by the method of repeated mitotic selection (TOBEY et coll 1967 ETTERSEN et coll 1977 b) After selection the synchronized populations were seeded nto plastic flasks (Nunclon or Falcon) and allowed to grow for the time required to each the stage at which they were to be irradiated Then they were loosened by a mild trypsin treatment 0 25 per cent trypsin solution (Difco 1 250) (PUCK et coll 957) for about 4 minutes

The irradiation techniques have been described previously (PETTERSEN et coll 977 a) Briefly the cells were irradiated at room temperature with 220 kV roentgen ays (1 6–1 9 Gy/min) in suspension in contact with a gas mixture of 97° N and CO_2 containing less than 4 ppm O

To irradiate mitotic cells the population was cooled to 0 C immediately after selection in order to prevent division Thereafter degassing was performed in the stainless teel irradiation chamber which was pre-cooled but kept at room temperature during degassing This procedure resulted in a gradual increase in temperature during

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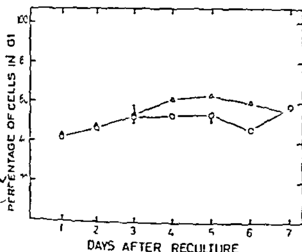


Fig 3 Fraction of cells in G1 for weekly recultured populations of NHIK 3025-cells These data were a result of mathematical analysis of DNA histograms like those shown in Fig 2. Each point represents the mean value from two parallel flasks, and the spread is indicated by vertical bars whenever exceeding the size of the symbols (0) medium changed on days 2 and 4 (_) medium not changed

Results

Increase in cell number Cell cycle and phase durations of synchronized exponentially growing populations have been given previously (PETTERSEN et coll 1977 a, b) (G1 6 5 h S 8 h G2–mitosis 3 5 h)

The relative increase in cell number appears in Fig 1 both for frequently recultured and weekly recultured populations The frequently recultured population has a constant doubling time of about 18 hours (PETTERSEN et coll 1977 b)

For the weekly recultured population however the rate of increase in cell number varied throughout the period of 7 days after reculturing (due to cell loss reliable observations were possible only up to 5 days) During the 24 hour period between ½ and 1½ days after reculture the cell number increased about 4-fold indicating a mean doubling time of about 12 hours during this period (the fraction of mitoses dividing into more than two daughter cells was negligible) After 3 to 4 days the cell number no longer increased and plateau phase followed

The distribution of cells on the different phases of the cell cycle was found from DNA histograms of samples taken every day during the 7 day growth of the weekly recultured populations In Fig 2 histograms are given for populations at 3 5 and 7 days after reculture Some variation in cell cycle distribution is present during the first 3 days when the population is in log phase but the variation is small later when the population is in plateau phase The fraction of cells in G1 can be accurately determined from the DNA histograms and is especially interesting from a radiobiologic point of view since G1 cells represent the most resistant subpopulation of exponentially growing NHIK 3025 cells (PETTERSEN et coll 1977 a)

The variation in the fraction of cells in G1 is shown in Fig 3 for weekly recultured populations which have or have not received change of medium on days 2 and 4 The data indicate that the fraction of cells in G1 varies between about 40 and 60

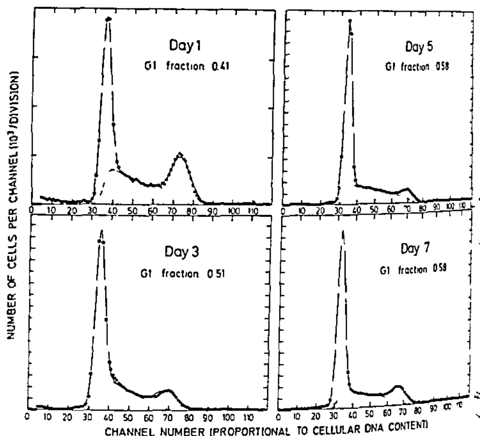


Fig 2 DNA histograms of NHIK 3025-cells from weekly recultured populations at various times after reculturing The histograms represent cells from flasks parallel to that counted for increase in cell number in Fig 1 Medium was changed on days 2 and 4 The fraction of cells in G1 is indicated as obtained by fitting of a mathematical model (fully drawn line) The broken line is the model's estimate for the distribution of cells in S (Gauss broadened first degree polynomial)

degassing and the temperature during irradiation was close to room temperature. The mitotic index was about 70 per cent during irradiation

Growth curves were recorded in an inverted microscope by repeated countings of the cell number within delineated areas on the bottom of the culture flask (PETTERSEN et coll 1977 b)

DNA histograms were recorded with a laboratory built flow cytometer (LINDMO & STEEN 1977 LINDMO & PETTERSEN 1978 PETTERSEN et coll 1977 b) Cells were stained for DNA measurement with ethidiumbromide (Calbiochem) (10 μg ml in TRIS buffer) after ethanol fixation (70°) and treatment with RNAse (BERKHAN 1972 LINDMO & PETTERSEN) The 488 nm line of the 4W Argon laser light source was used for excitation of ethidium bromide fluorescence which was measured at wavelengths longer than 525 nm Recorded DNA histograms were analyzed by means of a mathematical model (DEAN & JETT 1974 LINDMO & PETTERSEN) to obtain the fractions of cells in G1 S and G2 + mitosis

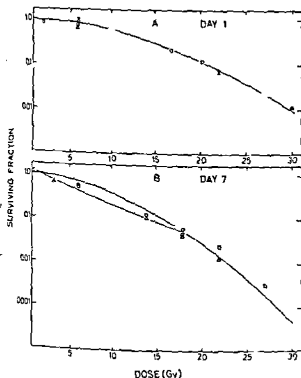


Fig 4 Survival curves for NHIK 3025-cells from weekly recultured populations irradiated 1 or 7 days after reculturing Each type of symbol represents one separate experiment The curves have been fitted by the method of least squares The linear quadratic equation was fitted to the data for 1 day old populations The data for 7 day old populations were analyzed in two ways a straight line was fitted to the data in the low dose region (up to 18 Gy) and the linear-quadratic equation was fitted to the data in the whole dose region Both curves are shown

are not shown but the parameters of all the curves (including that for 3 day old cultures) appear in Table 1 The data in the initial dose region (up to 18 Gy) for cells irradiated 7 days after reculturing were also fitted by a straight line (parameters given in Table 2) Apart from the difference in curve shapes the data indicate that cells from the 7 day old cultures (plateau phase) are more sensitive than cells from the 1 and 3 day old cultures (log phase)

Survival curves for cells from frequently recultured and synchronized populations Survival curves for frequently recultured populations are given in Fig 5 A The linear quadratic equation (1) fits well to the data and the line drawn represents the fit by the method of least squares The parameters are given in Table 1

Dose response curves for synchronized cells irradiated in G1 S G2 and mitosis are given in Fig 5 B All curves except the one for mitotic cells fit well to the linear quadratic equation For radiation doses higher than 10 Gy cells irradiated in G1 are less sensitive than cells irradiated in other phases of the cell cycle The mitotic cells are most sensitive However since there is a resistant fraction of G1 cells among the mitotic cells it may be expected that only the initial part of the curve actually represents mitotic cells

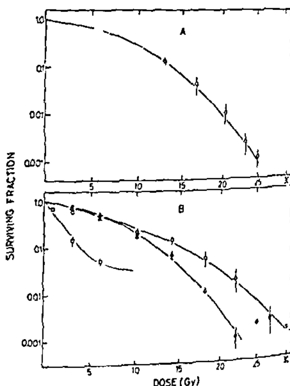


Fig 5 Survival curves for frequently recultured (exponentially growing) NHIK 3025-cells (A) and of NHIK 3025-cells synchronized by mitotic selection from frequently recultured populations (B) All curves represent best fits of the linear quadratic equation (1) The data for cells irradiated in G2 represent only one single experiment The remaining experimental points represent mean values from 3–5 different experiments Standard errors are shown by vertical bars provided they exceed the symbols ○ G1 4 h △ S 12 h + G2 15 h □ mitosis 0 h

Discussion

Growth kinetics The growth curves of Fig 1 indicate the difference in growth characteristics between NHIK 3025 cells seeded from a population in plateau phase (weekly recultured population) and those seeded from a population in exponential growth (frequently recultured population) Even during log phase the growth kinetics of the weekly recultured populations are different from that of the frequently recultured populations During log phase cells of the weekly recultured populations have a doubling time which is reasonably constant only over a period of 1 to 2 days Furthermore the lowest doubling time is 12 hours which is 6 hours shorter than that of the frequently recultured populations

The frequently recultured populations showed constant cell cycle kinetics over several weeks even months and therefore satisfy the definition of balanced growth of ANDERSON et coll (1967) For the weekly recultured populations the data indicate that the doubling time varies to some extent throughout the whole period between reculturing even within log phase

This variation in growth rate is not caused simply by a partial synchrony of the weekly recultured populations The DNA histograms in Fig 2 show that the fraction of cells in G1 is almost constant even in the period between 1 and 4 days during which the growth rate changes markedly

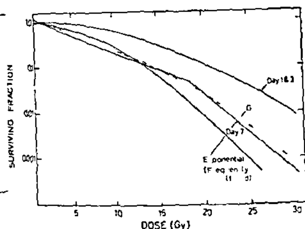


Fig 6 Dose response curves of NHIK 3025-cells from weekly recultured populations and from frequently recultured populations redrawn without experimental points For comparison the dose response curve of cells in G1 (---) representing the least sensitive sub-population of the frequently recultured population is al o included

Survival curves The variation in radiation response of the weekly recultured populations is also shown not to be a result of partial synchrony In Fig 6 the survival curve for frequently recultured populations is redrawn together with those of 7-day and 1 and 3 day old cells of the weekly recultured populations In addition the dose response curve of G1 cells representing the least sensitive subpopulation of the frequently recultured populations is shown for comparison The data indicate that th cells from weekly recultured populations in log phase (1 and 3 day old) are the least sensitive even less so than the G1 cells of frequently recultured populations

Data on the radiation response of mammalian cells in culture irradiated under hypoxic conditions in plateau phase and in log phase have previously been presented by BERRY et coll (1970) They used Chinese hamster CHL F cells and human HeLa (S3) cells and induced plateau phase either by overcrowding (CHL F) or by nutrient deficiency (both CHL F and HeLa) Generally they found that under hypoxic conditions cultures in plateau phase were more sensitive than cultures in log phase On this point their data agree with the present data Although curve shapes are difficult to compare it may also be mentioned that the HeLa cells in plateau phase produced an exponential survival curve in the dose range below 10 Gy (BERRY et coll 1970) and that the 7 day old NHIK 3025 cells also produced a dose response curve with an exponential part within the same dose range

Weekly recultered populations of NHIK 3025 cells in density inhibited plateau phase (7 days) seem to have inactivation kinetics slightly different from both log phase cells and cells in continuous exponential growth (frequently recultured) The survival curve for the 7 day old populations seems also to be well fitted by a straight line in the initial dose region (Fig 4) The shape of this survival curve is parallel to that published previously for asynchronous NHIK 3025 cells (PETTERSEN et coll 1973 1974 a experiments performed in 1972 and 1973 Fig 7) In Fig 7 all the data from previous experiments which were performed with 1 and 2-day old

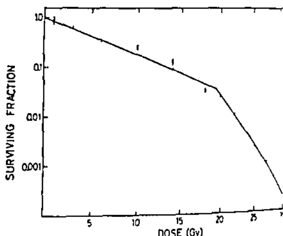


Fig 7 Data from previous experiments with NHIK 3025-cells (Pettersen et coll 1973 1974 a b) The data represent 9 different experiments performed in 1972 and 1973) In these experiments cells mainly from 1 and 2 day old weekly recultured populations were used In two experiments cells from 4 day old weekly recultured populations were used but these results did not differ significantly from the others

cells of weekly recultured populations are redrawn and fitted with two exponential lines The parameters of the initial exponential line appear in Table 2 both for the recent experiments with 7 day old populations (Fig 4) and for the previous experiments with 1 and 2 day old populations (Fig 7) Although the data represent populations of different age and even in different phase of growth they are similar This sums up to the following weekly recultured populations in log phase showed in 1972 and 1973 a radiation response which is similar to that found in 1976 for weekly recultured populations in plateau phase And this response is clearly different from that of weekly recultured populations in log phase in 1976 The reason for this change from 1972 to 1976 is not known A recent report by Elois et coll (1977) indicating seasonal variations in sensitivity of cells in culture may represent a hint that variation in sensitivity with time is a general phenomenon caused by factors which are so far unknown

Conclusions

(1) The cell cycle duration of cells of weekly recultured populations in log phase was found to be quite different from the cell cycle duration for cells which had been growing exponentially (frequently recultured) over several passages

(2) Cells from weekly recultured populations in log phase were less sensitive to radiation than cells from frequently recultured populations Since the weekly recultured population was even less sensitive than the least sensitive subpopulation in the frequently recultured population (G1) this difference was not caused by partial synchrony in the weekly recultured population

(3) In line with the observation reported by Hahn (1968) on cells of another line (Chinese hamster HA 2) the sensitivity of NHIK 3025 cells from weekly recultured populations irradiated while in log phase was different from that of such cells irradiated while in plateau phase The survival curve for cells from weekly recultured

populations in plateau phase (7 days) was similar to that published previously Pettersen et coll 1974 a) for cells from 1 and 2 day old weekly recultured populations This similarity is unexpected since the 1 and 2-day old populations used in previous experiments would be expected to be in log phase

Acknowledgements

The authors wish to thank Sidsel Greff Johansen for her excellent technical assistance This investigation was supported by grants from The Norwegian Cancer Society

SUMMARY

Cell cycle kinetics and radiation response under hypoxic conditions were analyzed with human cells of the line NHIK 3025 The cells were either kept in continuous exponential growth by frequent reculturing or went through log and plateau phase for each passage (recultured weekly) The cell cycle time for weekly recultured populations in early log phase was shorter than for cells in continuous exponential growth Cells in continuous exponential growth were more sensitive to radiation than cells in log phase The difference in sensitivity was not due to partial synchrony of weekly recultured populations

ZUSAMMENFASSUNG

Die Zellzykluskinetik und die Strahlenrespons wahrend hypoxischer Bedingungen wurden untersucht bei humanen Zellen der Linie NHIK 3025 die sich entweder im anhaltenden exponentiellen Wachstum befanden oder die log und Plateau Phase wahrend jeder Passage durchlief Der Zellzyklus war kurzer bei Zellen in der fruhen log Phase als fur Zellen wahrend des anhaltenden exponentiellen Wachstums Die Zellen in dem konstanten exponentiellen Wachstum sind mehr strahlensensitiv als Zellen in der log Phase Dieser Unterschied in der Sensitivitat ist nicht die Folge einer teilweisen Synchronie

RESUME

La cinétique du cycle cellulaire et la response aux radiations sous conditions hypoziques les cellules humaines de souche NHIK 3025 ont été etudiées Les cellules furent cultivées soit de façon de multiplication constamment exponentielle ou de façon q ils passent de la phase logarithmique au plateau avant d etre recultivees Le cycle cellulaire des cellules au debut de la phase logarithmique était plus court que ce des cellules en multiplication constamment exponentielle et ces dernières etaient plus sensibles aux radiations que les cellules de la phase logarithmique La difference de sensitivite est résultat d autre facteurs q un synchronisme partiel

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ROM THE DEPARTMENTS OF HOSPITAL PHYSICS AND NEURORADIOLOGY AND THE INSTITUTE OF RADIATION PHYSICS KAROLINSKA SJUKHUSET S 104 01 STOCKHOLM SWEDEN

RADIATION DOSE RELATED TO COLLIMATOR GEOMETRY IN THE FIRST GENERATION EMI SCANNER

BERTIL AXELSSON and MATS BERGSTRÖM

The radiation dose to a patient at CT examination of the head is small compared to the dose levels associated with other radiologic procedures The distribution of the dose within section 0 005 to 0 03 Gy (1 Gy = 100 rad) is well documented (PERRY & BRIDGES 1973 DAVIS & PRESSMAN 1974 BERGSTRÖM 1975 GLENN et coll 1975 SHERWOOD et coll 1975 McCULLOUGH et coll 1976) but not the dose distribution outside the section The dose gradient in this direction reflects the collimator design and the stray radiation and is of importance in assessing the dose to tissue adjacent to the section It also raises the question whether the design of the collimators is optimized with respect to utilization of the radiation

Radiographic equipment should be constructed to minimize the risk for accidental overdose to the patient Therefore the analysis was performed to find out what dose the patient might be exposed to in case of certain types of malfunction of the scanner

Material and Methods

The radiation doses from an EMI Mark I CT scanner were measured A 13 mm collimator standard settings 120 kV 33 mA and 5 min of scanning time were employed The doses were measured with LiF TL-dosimeters (high sensitivity ribbons) with the dimensions 3 mm 3 mm × 1 mm and also with roentgen film The LiF-dosimeters were individually calibrated against ^{60}Co and read off on a Harshaw

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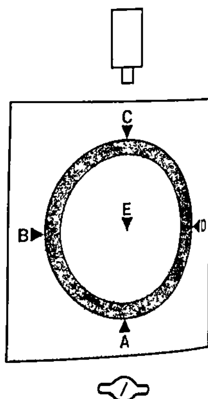


Fig 1 Positions for dose measurements

2 000 instrument with methods currently applied Correction for energy dependen- of the dosimeters was made assuming the effective energy of the beam to be 70 keV, implying a factor of 1 3 (RUDÉN 1975) The overall accuracy in the determina- tions of absorbed dose is estimated to be ±20 per cent

For measurement of the dose at various distances from the section a water filled plexiglass cylinder with 20 cm diameter was inserted in the scanner On three locations (B E D Fig 1) dosimeters were placed 2 by 2 with 10 mm axial separation. Regular films exposed at the same positions demonstrated the position and width of the slice The films were scanned with a densitometer and the full width half maximum (FWHM) determined

The scanner was operated with the tube in a fixed position irradiating in direction A to C for 5 min The doses were measured in positions A and C with the dosimeters well centered in the beam The size of the beam was measured on films in positions A and C and also at the upper collimator The beam width at the collimator was compared with the geometrical size of the aperture of the collimator

By turning off the index the tube could be made to scan for 5 min without rotation Doses and widths of the beam were measured with dosimeters and on film at posi- tions A B C

The dose to the thyroid gland was measured in 6 patients 5 adults and one child

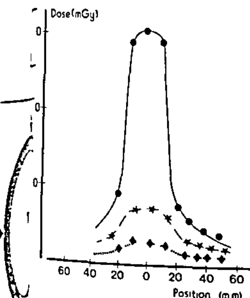


Fig 2 Dose measurements across the section at three different positions B (●) E (✱) and D (◆) in Fig 1 Point symbols indicate LiF dosimetry values and solid lines film densitometry calibrated against the dosimeter readings

wo dosimeters were placed on each patient on the skin over the thyroid with 5 cm acing during an ordinary skull examination with four scanning sequences pplying PMC with a scanning time of 6 5 min for each scan for the adults and min for the child

For calculations of detector geometry the size of the tube focus was depicted by a inhole-camera with an aperture of 0 1 mm

Results

The variations of the dose across the slice for three positions (B E D) appear Fig 2

The FWHM values were in position B 27 mm in E 47 mm and in D 55 mm With the tube stationary in the starting position the dose at A was 2 7 Gy and the ose at C 0 015 Gy The cross sectioned area of the beam measured on films was n A 24 mm × 3 2 mm and in C 36 mm × 5 4 mm (FWHM) Close to the collinator on the detector side the area was 40 2 mm × 5 8 mm (FWHM Figs 3 4) With the tube detector system traversing but not rotating in the same position the lose at A was 0 06 Gy at B 0 006 and at C 0 001 Gy The area of the irradiated egion as measured on films was 25 mm at A and 43 mm at C

The measurements of the dose to the thyroid in 5 adults yielded a mean of 0 7 mGy range 0 2 to 1 8 the comparable dose to the thyroid from a cerebral angiography s in the order of 3 mGy (BENGTSSON et coll 1976) and for the child 2 mGy The dosimeter to the right of the supine patient indicated a dose on the average 30 per cent higher than the opposite one

Fig 3 Film image of cross sectional area of the beam at the detectorside collimator

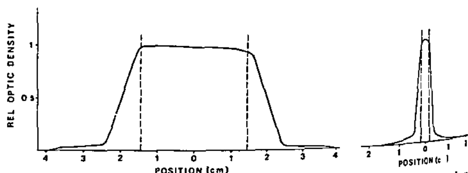


Fig 4 Densitometer readings of the film of Fig 3 along (left) and across (right) plane of the beam Vertical lines indicate the size of the collimator

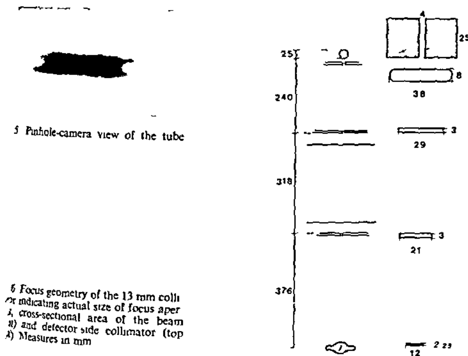
The size of the focus on the film exposed with the pinhole-camera (Fig 5) was 12 3 mm × 2 2 mm (according to the manufacturer s specifications it should be 12 mm × 2 25 mm)

The collimator geometry of the EMI Mark I scanner is illustrated in Fig 6 The design can be regarded as a compromise between demands partly contradictory (1) In order to give low noise in the signal as many photons as possible should be the detector (2) To give good geometric resolution the beam should be narrow (3) Scattered radiation should be stopped by the collimators and (4) The primary photons which have not been attenuated should preferably all reach the collim in order to keep the dose as low as possible

To satisfy condition 1 the collimators are made high 21 mm and 29 mm and a large focal spot is used To give a resolution in the order of millimeters the collimators are made 3 mm wide which also reduces scattered radiation

The use of a large focal spot increases the penumbra effect and hence impairs d fin tion of the beam The upper collimator of the scanner is made small enou h t avoid the penumbra region (Figs 3 4) This means that some radiation is was giving the patient a higher dose without contributing to the information

The fraction of photons used is expressed by the quotient E = b/p (b = number of primary photons hitting the detector p = number of primary photons passin the patient A crude calculation from the detector geometry and a measurement (Fig 4) gave the same result 40 per cent of the photons passing the patient al o pass the



5 Pinhole-camera view of the tube

6 Focus geometry of the 13 mm colli ... or indicating actual size of focus aper ..., cross-sectional area of the beam ...) and detector side collimator (top ...) Measures in mm

...ctor collimator The spacing of 4 mm between the detectors further reduces E 13 per cent to 0 35 Thus 35 per cent of the photons that have passed the patient utilized This relatively low efficiency is largely due to the broad penumbra region The divergence and penumbra of the beam are accessible from the width of the ...m at different positions These two factors together with scattered radiation ... leakage of radiation form the dose distribution (Fig 2) Scanning and rotation ... produce a dose distribution that is not rotationally symmetric The thyroid ...s chosen for dose measurements to exemplify the dose to a sensitive organ close to ... section The dose in the vicinity of the section will be of greater importance in ...ole body scanning as the dose to the gonads has to be considered

Th... doses that may be imposed to the patient under two different conditions of ...lty handling or malfunction of the scanner were also measured With the tube ...maining stationary for 5 min the maximum dose may be 2 70 Gy which for the ...s of the eye may be serious Simply pressing the WARM UP button instead of ... SCAN button on the panel makes possible such a dose As the buttons are ...ted close to each other it is advisable to put a cover over the WARM UP botton ...en it is not used Some of the newer CT scanners have other safeguards to prevent ...cidental irradiation of the patient in the warm up period

If the rotation of the scann... is not functioning the maximum dose to the patient ...ay be 0 06 Gy This may happen if for instance the computer stops The traverse ...ovements will then contin... in the same angle and the tube emission continues

SUMMARY

The radiation dose from the first generation EMI scanner has been analysed including the variation of the dose perpendicular to the section the dose dependence of the size and collimation of the beam and the fraction of radiation passing the patient and utilized for information The possible dose in case of malfunctions of the scanner was also measured

ZUSAMMENFASSUNG

Die Strahlendosis der ersten Generation von dem EMI Scanner wurde analysiert einschliesslich der Variation der perpendikularen Dosis zum Schnitt der Dosis Abhängigkeit der Grosse und Kollimation des Strahlenganges und der Strahlenfraktion die den Patienten passiert und fur die Information verwendet wird Die mogliche Dosis bei Fehlerfunktionen des Scanners wurde auch gemessen

RESUME

La dose de radiation emise par le Scanner EMI de première generation a été étudiée, y compris la variation de la dose perpendiculairement a la coupe la dépendance de la dose par rapport aux dimensions et à la collimation du faisceau et la fraction du rayonnement traversant le malade et utilisée pour l information Les auteurs ont aussi mesure les doses possibles dans les cas de mauvais fonctionnement du scanner

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THYROID GLAND VOLUME ESTIMATED BY USE OF ULTRASOUND IN ADDITION TO SCINTIGRAPHY

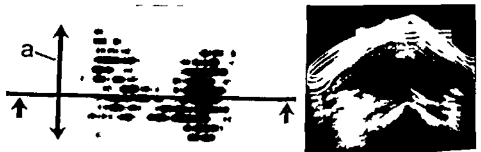
MALCOLM C BROWN and RALPH SPENCER

In the treatment of thyrotoxicosis with radioactive iodine the volume of the gland an important factor influencing the dosage A one plane image of the gland can be btained by scintiscanning Methods to estimate the size of the thyroid gland from e scintiscan were put forward by ALLEN & GOODWIN (1952) and later by HIMANKA LARSSON (1955) The formula evolved by the latter authors Volume $= \frac{1}{3}$ A^3 cm^3 A = area in cm^2 of the scintiscan) has been accepted as the most reliable guide to olume assessment However inaccuracies of the method arise due to the irregular hape of the gland the absence of information concerning the thickness of each lobe nd the effect of foreshortening due to the curve of the anterior surface of the neck

The width length and thickness of the thyroid lob s were measured from ultra onic scans of the anterior aspect of the neck by HULSE et coll (1972) The volume f each lobe was estimated using a standard geometric formula volume of an oid $= (\pi/6) a \times b \times c$ (where a b and c represent height width and thickness) wenty-one cadavers were scanned immediately before autopsy and in each case the olumes were directly measured by liquid volumetry

YAMAKAWA & NAITO (1966) used planimetric measurements of serial ultrasonic cans to estimate the gland size However there are sometimes difficulties in estimating he longitudinal limits of the thyroid tissue on the ultrasonic scan and a reference to he scintiscan is useful in removing ambiguities concerning these limits An extra ource of difficulty with the ultrasonic method is the intervention of the clavicle or he anatomic limitation presented by the clavicle

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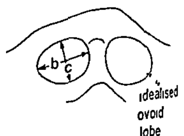


Fig 1 ^{131}I scintiscan (level of ultrasonic scan †) and ultrasonic scan (largest section) Length (a) breadth (b) and depth (c) measurements of the left lobe For the ultrasonic scan the bistable display gives a clear delineation of the boundaries of the gland The gland mass estimations were as follows specimen plus surgeon s estimate of gland remnant 56 g from scintiscan using the formula of Himanka & Larsson 21 g breadth and depth from ultrasonic scan and length from scintiscan 58 g

The object of this report is to show that it is possible to obtain a more accura assessment of the thyroid volume using a combination of the scintiscan and the ultrasonic scan The scintiscan usually gives a more accurate estimate of the height of each lobe but fails to assess the thickness of the tissue the ultrasonic scan supplies information related to the thickness of tissue and irregularities which cannot otherwise be demonstrated

Method

In 60 patients thyroid function tests scintiscan and ultrasonic scan were performed and the specimen was examined and weighed in the pathology department

For each case the area of uptake on the scintiscan was measured by countin the squares on a superimposed millimetre grid The mass of the gland was calculated from this area by the formula of HIMANKA & LARSSON

Ultrasonic scans were made on each patient at 1 cm intervals down the neck to produce a series of sectional images These were p rformed by contact scanner using a Nuclear Enterprises Ltd (Sight Hill Edinburgh U K) NE4102 with a 5MHz flat probe Images were recorded on Polaroid 107 film from a bistable oscilloscope The ultrasonic scan showing the largest transverse section through the gland was selected and the two lobes sketched as ellipses Diameters b and c were measured for each lobe (Fig 1) The length (a) was measured from the scintiscan The length of each lobe was often known from the number of 1 cm spaced ultrasonic sections which were possible but the value of (a) from the scintiscan was used if it was larger

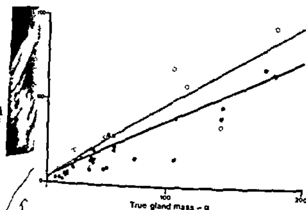


Fig 2 Comparison of mass estimation by the two methods Open dots scintiscan solid dots combined scintiscan/ultrasonic method Linear regression lines have been drawn to the formula y = mx + b Solid line represents the scintiscan results (m = 0 73 b = 3 41 r = 0 77) broken line results of combined scintiscan/ultrasonic method (m = 0 93 b – 2 94 r = 0 92)

-han the ultrasonic result The volume of each lobe was calculated from the ovoid ormula

From the surgical results the mass of the gland was estimated by weighing the xcised mass and adding to this the surgeon s estimate of the remaining portion of he gland This latter estimate was usually about 5 g for each lobe However there till remained unavoidable inaccuracies in the estimation of the removed mass due o loss of blood and colloid material during surgical procedures

Results

The results of the gland mass estimation from the scintiscan area set against those rom surgical findings appear in Fig 2 as well as the values estimated using the combined ultrasonic scintiscan method The linear regression lines on Fig 2 indicate hat an evident improvement in the gland mass estimation has been achieved by the se of the combined method However the parameters of the new line (m = 0 93 b = 2 94 r = 0 92) show slightly less favourable correlation with the surgical findings in the 60 patients than HULSE et coll found from their 21 cadavers (m = 0 96 b – 1 5 r = 0 989)

Expressing the gland mass estimations as percentages of the values found at surgery it was found that the average was 79 5 per cent for the scintigraphic method, with SD of 51 3 per cent The range of the results extended from 13 6 to 336 per cent The method using combined ultrasonic and scintiscan measurements gave an average r sult of 100 4 per cent SD 34 5 per cent The range extended from 45 1 to 281 per cent

These results show clearl that the combined method is more accurate than the scintiscan method alone i terms of the average result and in terms of standard deviation and range

O the results presented ere to use the HIMANKA & LARSSON formula a correction is required in the coeffic nt making the formula V – 0 419 $A^{3\ 2}$ However in view

of the large scatter of results even this corrected figure may still not yield reliable values particularly in those cases in which the two lobes are not at all equal in size.

More rigorous methods of volume estimation from the ultrasonic scans have been prepared e g that by RASSMUSSEN & HJORTH (1974) in which the volume is calculated from the sum of the area on each section scan The present method is less mathematically accurate but may have more practical application The results shown on Fig 2 appear to justify this simplification

Conclusion

This simple approach to estimation of gland volume by combining ultrasonic and scintigraphic scans has been justified by the good correlation between the estimated volumes and the surgical findings

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We wish to thank consultants who have referred the cases and allowed us to make use of their clinical records We are especially indebted to Mr Paul Atkins Consultant Surgeon at the David Lewis Northern Hospital and to Mr David Sykes at Walton Hospital and also to the technical staff of the Liverpool Clinic for the thyroid function tests and scintiscans. We also acknowledge the financial help given to us by the Endowment Fund of the Liverpool Clinic and Clatterbridge Hospital and the Research Fund of the Mersey Regional Health Authority

SUMMARY

The method of estimating the mass of the thyroid gland from the area of the scintigraphic image has been compared with a method combining ultrasonic with scintigraphic images The results for both methods were compared with surgical findings and the scintiscan method alone was found to produce estimates which were on an average 79 5 % of the surgical results The corresponding estimates for the combined method were on average 100 4 %

ZUSAMMENFASSUNG

Die Methode zur Bestimmung des Thyreoidea Volumens von der szintigraphischen Flache wurde mit einer Methode die aus der Kombination von Messungen von Ultraschall und szintigraphischen Scans besteht verglichen Die Resultate beider Methoden wurden mit den chirurgischen Ergebnissen verglichen Die szintigraphische Methode ermöglicht Bestimmungen die im Durchschnitt 79 5 Prozent der chirurgischen Resultate entsprachen Die entsprechenden Bestimmungen mit der kombinierten Methode waren im Durchschnitt 100 4 Prozent der chirurgischen Ergebnisse

RESUME

Les auteurs ont pu determiner la precision de l estimation du volume thyroidien à partir de la surface scintigraphique et a partir d une association de mesures sur des scintigraphies

des échotomographies Ces estimations ont été comparées avec les resultats opératoires
*s estimations scintigraphiques etaient en moyenne de 79 5°o des résultats chirurgicaux
*s estimations associant l échotomographie et la scintigraphie étaient en moyenne de
)0 4 des résultats chirurgicaux

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FROM THE DEPARTMENT OF RADIOLOGY, TORONTO WESTERN HOSPITAL, TORONTO, ONTARIO M5T 2S8 CANADA

COMPACT BONE MINERAL DENSITY OF THE NORMAL HUMAN RADIUS

H Erik Meema and Silvia Meema

Following the introduction of gamma ray absorptiometry by Cameron & Sorenson (1963) for in vivo measurement of bone mineral mass in the radius and the subsequent developments and modifications of this technique (Karjalainen 1973 Greenfield et coll 1975) considerable data have been accumulated (Mazess & Cameron 19 3 Alhava & Karjalainen 1973 Karjalainen & Alhava 1977) These methods determine the bone mineral mass of a cross sectional slice of bone per unit length (g/cm) In addition a ratio of this mass to the external diameter of bone is usually also calculated (in g/cm) but until recently determination of true bone mineral density (i e the amount of mineral per unit volume of cortical bone in g/cm³) has not been attempted with gamma ray absorptiometry The feasibility of calculating bone mineral density by measuring the cortical bone mineral mass with gamma-ray absorptiometry together with planimetic radiographic measurements of the same area has been suggested by three authors (Karjalainen Alhava & Karjalainen Greenfield et coll Meema et coll 1976 Karjalainen & Alhava) However only Alhava and Karjalainen (1973 1977) have published sufficient normative data for cortical bone mineral density in the radius and ulna

Roentgen ray photodensitometric findings for the proximal shaft of the radius including determinations of cortical bone mineral density in normals and in some metabolic bone diseases have previously been reported (Meema et coll 19… Meema & Meema 1969 1970 1972) Since these findings differ considerably from

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ABDOMINAL RADIATION RESPONSE MODIFIED BY HYPOXIA AFTER INTRA AORTAL INJECTION OF STARCH MICROSPHERES

Experiments in the rat

J O FORSBERG and B JUNG

Tissue oxygenation has been of major interest in radiation therapy ever since the importance of dissolved oxygen for the radiation effect was first pointed out (cf GRAY et coll 1953 VAN DEN BRENK 1969) One mode of abolishing the effect of tumour hypoxia is to use radiation qualities giving a high linear energy transfer (neutrons negative pi mesons etc) (FOWLER 1966) Alternatively as discussed in th following oxygen deprivation may be useful provided that hypoxia can be induced in the normal tissues situated in the high dose volume (cf GRAY et coll 1967 CHURCHILL DAVIDSON 1967) Several techniques for clinical and experimental use of hypoxia have been tried with this principle in mind viz instillation of nor epinephrine and sodium sulphite in the rectum (LARSSON & STENSON 1965) arterial clamping with tourniquets (VAN DEN BRENK et coll 1966 SUIT & LINDBERG 1968) or snares (PENN et coll 1975) and the intra arterial infusion of epinephrine (STECKEL et coll 1969)

Starch particles that are degraded by endogenous blood amylase (ARFORS et coll 1976) offer a new method of achieving temporary local ischemia Such microspheres are injected intra arterially at a suitable site and then become trapped in the

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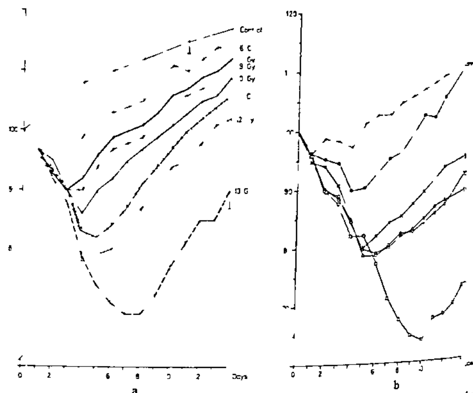


Fig 1 a) Body weight development in survivors Per cent of original weight durin 14 days after single-dose abdominal irradiation of non protected non laparotomized animals Mean and SEM. b) Results from an experiment closely similar to that reported in Fig 1 a) but with 250 kV roentgen rays (0 6 mm Cu HVL 13 mm Cu and dose rate 0 43 Gy/min (Data redrawn from BOND et co 1950) --- Controls ● 7 Gy 9 Gy ○ 10 Gy _ 11 Gy □ 13 Gy

arterioli so as to cause a complete transient blockage of the erythrocyte flow (FORSBERG 1978)

Previously (FORSBERG et coll 1978 a) hypoxia induced by degradable starch microspheres in the foot of the rat was found to give a dose modification factor of 0 50 i e the dose given to animals during hypoxia had to be twice that given to intact control animals to produce the same effect

The present investigation was undertaken to find out whether the protective effect of hypoxia brought about by degradable microspheres could be reproduced also in the rat gut The experimental model implied a retrograde catheterization of the aorta to the level of the superior mesenteric artery After irradiation of the abdomen with single doses of roentgen rays the weight development and presence of diarrhoea was followed in groups of protected and non protected rats

Material

Sprague Dawley male rats weighing about 300 g were used They were fed on a standardized diet and had free access to water and food before and after the

Table 1

Irradiation doses and number of animals in the different groups NPNL = non protected non laparotomized NPL = non protected laparotomized PL = protected laparotomized

Dose Gy	6	8	9	10	11	12	13	14	16	18
NPNL	6	6	6	6	6	6	6			
NPL						6		6		
PL				6		6		6	6	7

experiments Seven groups of non protected non laparotomized animals were irradiated with doses between 6 and 13 Gy (600–1 300 rad) Five groups of protected animals were irradiated with graded doses between 10 and 18 Gy Laparotomy was performed before irradiation Five groups served as controls One group had no treatment whatsoever one had laparotomy only one had laparotomy and administration of microspheres and two had laparotomy and irradiation with 12 and 14 Gy respectively Details about the groups are given in Table 1

Methods

The degradable microspheres (Pharmacia AB Uppsala Sweden) had a diameter $44 \pm 7 \mu m$ and were suspended in physiologic saline (80 mg/ml $6 \cdot 10^{9}$ spheres/ml) Suspensions of 6.75×10^{6} spheres in 20 ml buffered saline with 240 and 1 500 IU standard amylase gave in vitro degrading half times of 20 and 10 min respectively (NYGREN 1976) The blocking time of the gut circulation in the actual experimental model reached about 30 min (FORSBERG)

Operation and irradiation of each animal lasted for about 25 min and was carried out under intraperitoneal Mebumal sodium anaesthesia (ACO 40 mg/kg) administered 20 min before irradiation The time schedule was identical for all irradiated groups

For the introduction of starch microspheres an indwelling catheter (Portex PP 10) was introduced into the aorta via the femoral artery after an incision in the left groin The tip of the catheter was advanced to about 5 mm above the entrance of the superior mesenteric artery The catheter was filled with heparinized saline After vigorous shaking a suspension of 0.75 ml (4.5×10^{6} spheres) was injected through the catheter the injection time being about 30 s Via a midline [illegible] the gut was then inspected for ischemia Only animals demonstrating a p[illegible] [illegible]all in the major part of the gut typical for profound blockage (FORSBERG) [illegible] accepted The abdomen was then temporarily closed and the animal transfer[illegible] for irradiation After irradiation the catheter was removed and the wounds w[illegible] [illegible]hed After the experiments the animals were kept in separate cages

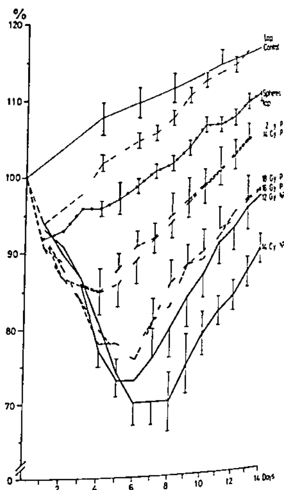


Fig 2 Single dose abdominal irradiation of non protected laparotomized and protected laparotomized animals Body weight development in per cent of original weight Curves are also given for untreated animals (control) only laparotomized and laparotomized and microsphere injected animals Mean and SEM

Irradiation A radiation field of 5 cm × 7 cm covered the abdomen from flank flank from the distal point of the sternum to the pelvis Irradiation was perform with 8 MV roentgen rays from a linear accelerator (MEL SL 75/10 600 pulse pulse length 2 μs mean dose rate 13 Gy/min source to skin distance 71 5 cm) Th entrance area was during irradiation covered with a 15 mm thick layer of pol styrene which gave adequate dose build up in the gut region Phantom experimen with radiation sensitive diodes (DPD5 Scanditronix Uppsala Sweden) reveale that the relative dose delivery was accurate to 1 per cent and that the dose was th same within 5 per cent throughout the irradiated region of the gut

Each irradiated animal as well as the controls was weighed 1 hour before irradi tion and then daily for 14 days at 24 h intervals Any signs of radiation sickne were looked for and the stools were also inspected at these times

Table 2

Maximum weight decrease in per cent of original weights in non protected non laparotomi ed (NPNL) non protected laparotomi ed (NPL) and protected laparotomi ed (PL) rats Mean ± SEM † indicates 1 dead animal

Gy	NPNL	NPL	PL
6	4 5±1 1		
8	9 8±0 9		
9	9 7±1 1		
10	14 4±2 1		15 0±0 8
11	18 2±3 1		
12	21 1±1 2	26 6±2 2 †	15 1±2 5
13	31 4±2 1 †		
14		29 6±3 1 †	13 9±3 3
16			24 3±4 9 †
18			21 8±3 0 †

Results

No non irradiated animals died during the observation period no diarrhoea occurred Among the irradiated groups 3 non protected and 2 protected animals died after developing heavy diarrhoea oliguria and exhaustion (Table 2)

The weight curves appear in Figs 1 a and 2 with data included also for the control groups In the non irradiated control groups it was found as expected that laparotomy necessary for inspection of the intestine for ischemia had a slight but significant influence on the weight curve The trauma of catheterization and the injection of microspheres enhanced this effect

The curves for the irradiated animals are characterized by initial weight loss down to a minimum l vel which was strongly correlated to the radiation dose The daily we ht loss in the initial period seems to be little dependent on the dose as does also the daily weight increase at a later stage Evaluating the dose modification factor from the weight curves it was found that the protected laparotomized 16 Gy and 18 Gy and non protected laparotomized 12 Gy groups were closely similar The dose modification factor related to the protective procedure could thus be roughly estimated to 0 7

Diarrhoea appeared with few exceptions on the third day irrespective of the radiation dose or of induction of hypoxia (Fig 3) All the surviving animals returned to normal stools before the end of the observation period and in most cases within 1 to 2 days after the occurrence of the minimum in the weight curve

Discussion

The lay out of the experiments with irradiation in situ of the gut implies that also other organs (spleen pancreas kidneys spine and part of the liver) were included

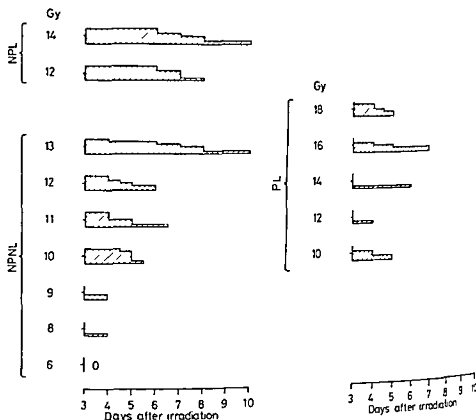


Fig 3 Frequency and duration of diarrhoea in the different groups after single-dose abdom[inal] irradiation NPNL = non protected non laparotomized NPL = non protected laparotomized, PL protected laparotomized animals

in the target volume The intestine itself should however be the critical organ und[er] the prevailing conditions (QUASTLER et coll 1951 QUASTLER 1963) Also at th[e] doses used in the experiments a significant influence on the body weight from th[e] effect on other organs irradiated would probably not manifest itself durin[g] the observation period

For the same reason any hypoxic protection of the other organs which were necessarily at least partially blocked after the aortic injection should not mark[ed]ly influence the results It is thus concluded that the main cause of the radiation eff[ec]t on the two variables followed—body weight and diarrhoea—was due to the injur[y] of the bowel

The blocking time is different for the various abdominal organs It can be inferred from flow analyses (FORSBERG) with tracer microspheres that the d[uo]denum the jejenum and the colon were likely to be poorly protected with th[e] amount of spheres injected These parts of the gut have a relatively high flow 5 m[in] after injection of the spheres The rather high value of the dose modification fact[or] (0 7) corresponding to an oxygen enhancement ratio of 1 33 may thus be explain[ed]

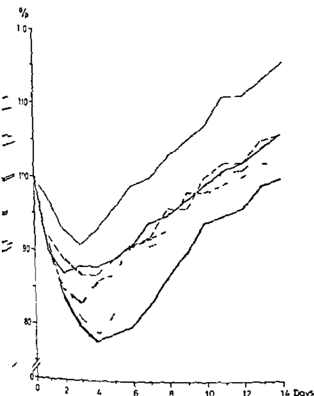


Fig 4 Single-dose abdominal irradiation of 10 Gy Body weight development in per cent of original weight in 6 animal during 14 days Periods of diarrhoea indicated by heavy lines

The sensitivity of the chosen indices of radiation injury obviously is rather high since dose differences of 1 Gy were most often clearly demonstrated in the rather small groups The weight curves from the non protected non laparotomized groups are similar to the curves achieved by BOND et coll (1950) who used the same breed of rats in evaluation of abdominal response to roentgen rays (Fig 1 b) A difference between the non protected and the protected animals is al o evident from a com parison of the data in Figs 1 and 2

From biologic work (MAISIN et coll 1971) it is well known that radiation doses at the level used in the present experiment give a maximum sloughing of the epi thelium on the third day in accordance with the observation that diarrhoea most quently started on that day

The weight loss is probably caused by radiation induced anorexia and catabolism and not critically dependent on the presence of diarrhoea as such (Fig 4) There is a sinking similarity in the weight development down to the minimum level and a corresponding similarity thereafter irrespective of whether diarrhoea was present or not.

The mechanism of inducing hypoxia with starch microspheres is a blockage at the level of the arterioles in the gut wall which implies that the collateral circulation

is abolished Theoretically, therefore this method would be superior to proximal clamping of the mesenteric artery (JERVIS et coll 1968 OSBORNE et coll 1970) which cannot exclude collateral circulation and hence cannot guarantee maximum protection

Furthermore a single injection of spheres gives adequate blockage and no continuous injection is necessary as with epinephrine and other vasoconstrictors, which also carry with them a certain risk of systemic complications

For a closer evaluation of the injury to the mucosa and post irradiation fibrosis an investigation on exteriorized gut is in progress

Acknowledgements

The investigation was supported by the Swedish Cancer Society The irradiation was performed at the Department of Oncology Akademiska Sjukhuset Uppsala

SUMMARY

Degradable starch microspheres were injected in the aorta of rats above the level of the superior mesenteric artery 5 min before roentgen irradiation of the abdomen The local hypoxia induced by the spheres was found to have an appreciable protective effect. The dose modification factor was estimated as 0 7

ZUSAMMENFASSUNG

Abbaubare Starke Mikrospharen wurden in die Aorta von Ratten oberhalb der Arteria mesenterica superior 5 Minuten vor Rontgenbestrahlung des Abdomens injiziert. Die durch diese Spharen hervorgerufene lokale Hypoxie gab einen wesentlichen Schutzeffekt Der Dosis Modifikationsfaktor wurde als 0 7 berechnet

RESUME

Des microspheres d amidon dégradable ont été injectees dans l aorte de rat au dessus du niveau de l artère mésentérique supérieure 5 minutes avant irradiation par des rayons de Roentgen de l abdomen L hypoxie locale induite par les sphères a eu un effet protecteur appréciable Le facteur de modification de doses a été estime à 0 7

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HISTIOCYTOSIS X

III Clinical value of serial biopsies

P FREDERIKSEN and P THOMMESEN

The possible development of disseminated histiocytosis from localised eosinophili granuloma has been discussed for more than 30 years and morphologic transitio s have been stated by ENGELBRETH HOLM et coll (1944) and AVIOLI et coll (196)

It has furthermore been shown that the microscopic appearance of histiocytosis X may be of prognostic significance (NEWTON & HAMOUDI 1973 FREDERIKSEN & THOMMESEN 1978) Only seldom have long term serial biopsies been reported (SCHAJOWICZ & SLULLITEL 1973) It is not known whether changes in the clinical condition are accompanied by microscopic changes in serial biopsies (LAHEY 197)

In a clinical material comprising 45 patients with histiocytosis X seri l biopsies were performed in 8 The present report will consider the microscopic appearances of these specimens

Material and Method

The 8 patients from the period 1945–1975 had a prolonged or divergent clinical course and 2 or more biopsies were performed with specimens availabl f r evaluation When necessary new sections were made The specimens were clas ified as either proliferative granulomatous xanthomatous or fibrous type of hist cytosis (ENGELBRETH HOLM et coll LEVER 1961)

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Table

Microscopic appearance in serial biopsies of 8 patients with histiocytosis X

Case No	Age (years)	Sex	Site of lesion and microscopic appearance					
			Biopsy 1	Biopsy 2	Biopsy 3	Biopsy 4	Biopsy 5	Time interval initial—latest biopsy
[illegible]	7	M	Osseous granulomatous	Cutaneous unchanged	Mucosal xanthomatous	Mucosal unchanged		3½ years
[illegible]	3	M	Lymphnode proliferative	Lymph node unchanged	Cutaneous unchanged	Cutaneous fibrous		3 years
3	3	F	Osseous proliferative	Mucosal unchanged	Cutaneous unchanged	Mucosal unchanged	Cutaneous unchanged	3 years
4	3½	F	Osseous proliferative	Cutaneous unchanged	Osseous unchanged	Mucosal unchanged	Cutaneous unchanged	2½ years
5	2	F	Mucosal proliferative	Osseous unchanged	Osseous unchanged			2 years
6	0	F	Mucosal proliferative	Mucosal unchanged	Lymph node normal	Lymph node Hodgkin	Spleen Hodgkin	1½ years
7	57	F	Osseous fibrous	Osseous unchanged	Lung sarcoma	Cutaneous sarcoma		9 months
8	4½	F	Cutaneous proliferative	Subcutaneous sarcoma				1½ years

Results

The age at initial biopsy the sex distribution and the sites and number of biopsies and their time intervals are given in the Table

In cases 1 and 2 a development towards a xanthomatous or fibrous lesion was found whereas in cases 3 4 and 5 no changes in the microscopic appearance were apparent Malignant lesions were observed in the latest biopsies from cases 6 7 and 8 and these cases are now reported

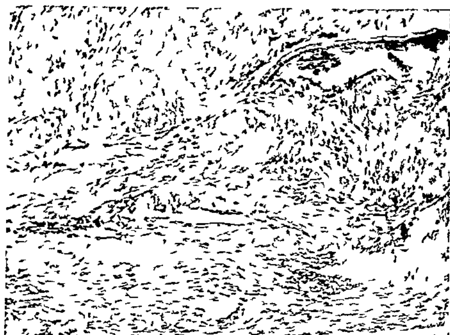


Fig 1 Case 7 Biopsy from an expanding and lytic bone lesion in the right humeral head and neck Fibrous tissue compatible with fibrous phase or healing of histiocytosis X. Hematoxylin Eosin ×120

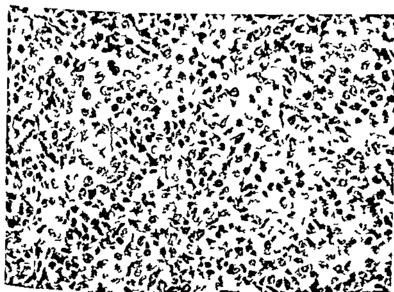
Case 6 The initial lesions were confined to the gingival mucosa and the mandible with loosening of the teeth Microscopy showed proliferative histiocytosis X composed of benign histiocytes eosinophils and lymphocytes Repeated mucosal biopsy 6 months later showed identical findings Due to pulmonary infiltrations mediastinal lymph nodes were biopsied, but no abnormalities were found After radiation therapy (20 Gy) the patient was symptom-free for 1 year Then swelling of cervical lymph nodes was observed and subsequent neck node biopsy revealed Hodgkin s disease The lymphoid tissue was replaced by an intermingling of eosinophils lymphocytes and atypical histiocytes some of these of Reed-Sternberg type with huge eosinophilic nucleoli At staging laparotomy nodular Hodgkin infiltrates were found in the spleen A lethal outcome resulted within one year At autopsy nodular tumour infiltrates in the liver lymph nodes and bone marrow were found The primary gingival lesion was fibrosed without microscopic evidence of tumour

Case 7 On admission to hospital multiple bone lesions were observed in the spine pelvis, femur and humerus Particularly a lesion in the right humerus suggested malignancy Several biopsies only revealed fibrosed stage of histiocytosis X Radiation therapy relieved symptoms for 3 months subsequently progression occurred with cutaneous and pulmonary lesions where biopsies now suggested malignant histiocytosis Lethal outcome occurred within 10 months Autopsy was not performed

Case 8 This patient had the Letterer Siwe syndrome diagnosed at 2 years of age At clinical examination cutaneous elements resembling seborrheic dermatitis and enlargement of the liver and spleen were found Radiography revealed typical lesions in the skull and the right femur Biopsies from the liver and a cutaneous element were compatible with histiocytosis X Remission occurred after treatment with chemotherapeutica Subsequently



a



b

Fig 2 Same case as Fig 1 a) Multiple nodular pulmonary infiltrates 6 months later than the biopsy shown in Fig 1 Sarcomatous cells were present in the fine needle aspirate b) Surgical biopsy from cutaneous and subcutaneous tumour 2 months later (l> elv packed histiocytes some with atypical nuclear features and some in mitosis Hematoxylin Eosin 300

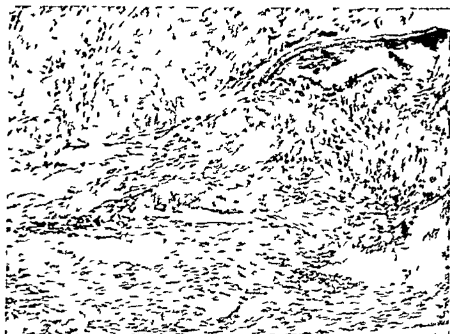


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a subcutaneous tumour about 4 cm in diameter was removed from the posterior surface of the left knee Microscopy then indicated malignant histiocytosis Two years later additional osseous lesions appeared in the skull The patient is alive with active disease 5 years after onset of the first symptoms

Discussion

In this selected series of serial biopsies 2 patients demonstrated a development of the morphologic appearance from initial proliferative lesion to late xanthomatous or fibrous lesion of histiocytosis X as suggested by ENGELBRETH HOLM et coll and AVIOLI et coll

In 3 other cases the microscopic appearance was unchanged which may be due to an insufficient observation period The most remarkable finding was that the lesions in 3 cases (6 7 and 8) took a malignant clinical course repeated biopsies revealing malignant lesions viz. malignant histiocytosis and Hodgkin s disease The distinction based on clinical and microscopic findings between Hodgkin s disease and malignant histiocytosis usually poses no difficulty (RAPPAPORT 1966 BYRNE & RAPPAPORT 1973 WARNKE et coll 1975) However both diseases are characterized by a proliferation of neoplastic histiocytes A wider designation of the histiocytic disorders has recently been proposed by CLINE & GOLDE (1973) In their opinion the histiocytoses are considered to represent a wide spectrum of diseases ranging from well differentiated histiocytoses (unifocal and multifocal eosinophilic granuloma of bone and Hand Schüller Christian disease) to poorly differentiated histiocytic disorders such as malignant histiocytosis reticulum cell sarcoma and monocytic leukemia

This concept may be supported by the present findings of morphologic transitions in the histiocytoses both between the various benign histiocytic lesions and particularly by the occurrence of malignant foci

Repeated biopsies in patients diagnosed as having histiocytosis X may therefore prove valuable especially in patients with a long clinical course when aggravation of the clinical condition occurs or when new foci appear

SUMMARY

In a retrospective review of sequential biopsies in 8 cases of histiocytosis X 2 developed xanthomatous or fibrous lesions 3 remained unchanged whereas 3 developed malignant disease one Hodgkin s disease and 2 malignant histiocytosis A possible progression from a benign well differentiated to malignant histiocytic lesion is discussed and the importance of achieving a microscopic diagnosis is emphasized

ZUSAMMENFASSUNG

Bei einer retrospektiven Untersuchung von Serien Biopsien in 8 Fällen von Histiozytosis entwickelte sich bei 2 xanthomatose oder fibrose Veränderungen, 3 verblieben unverändert, während sich bei 3 eine maligne Erkrankung entwickelte in einem Fall eine Hodgkin

sche Erkrankung und in 2 eine maligne Histiozytosis Ein moglicher Fortschritt von einer benignen gut differenzierten zu einer malignen histiozytären Veränderung wird diskutiert und die Bedeutung eine mikroskopische Diagnose zu erhalten hervorgehoben

RESUME

Une étude rétrospective de biopsies séquentielles dans 8 cas d histiocytose X a montre l apparition de lesions fibreuses ou xanthomateuses dans 2 cas le diagnostic est resté inchangé dans 3 cas alors que 3 cas ont présenté une maladie maligne un cas de maladie de Hodgkin et 2 histiocytoses malignes Les auteurs examinent la possibilite d une progression allant d une lesion histiocytique bénigne bien différenciée a une lésion maligne et ils insistent sur l importance de faire un diagnostic microscopique

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NEUROLOGIC COMPLICATIONS AFTER IRRADIATION OF MALIGNANT TUMORS OF THE TESTIS

ANNE VIBEKE SCHIODT and OLE KRISTENSEN

Radiation induced injury to nerve tissue unavoidably included in the irradiated areas during treatment of malignant tumors has been reported for both the peripheral (STOLL & ANDREWS 1966 SPIESS 1972) and the central nervous system

Several clinical syndromes have been distinguished in connection with the lesions arising after irradiation of the cervicothoracic spinal cord Transient radiation myelopathy (JONES 1964 BÆKMARK 1975) constitute one group with purely subjective symptoms in the form of paresthesias often Lhermitte s sign which disappear spontaneously within a few months Another group is marked by irreversible partial or complete transverse medullary lesions with spastic paresis loss of sensibility and bladder and rectum dysfunction On the basis of the course cases of acute radiation myelopathy have been described (BODEN 1948 PALLIS et coll 1961) in which the symptoms reached their peak within a few days However such an acute course is rare in most cases it is a question of a chronic progressive myelopathy developing over a period of months or years (REAGAN et coll 1968 PALMER 1972)

In connection with irradiation of the lumbar spine in the treatment of malignant testicular tumors GREENFIELD & STARK (1948) used the designation postirradiation neuropathy to describe a syndrome with flaccid paresis in the lower extremities but without sensibility disturbance and suggested that this could be the result of selective injury to anterior horn cells Judging from the literature this syndrome is uncommon Fifteen such cases have been described (MAIER et coll 1969)

Several authors have attempted to establish tolerance limits for the spinal cord at

Submitted for publication 28 April 1977

Table 1

Microscopic findings and clinical staging in the whole material and in patients alive at the follow up

	Clinical stage	No of patients	Alive at follow up	Neurologic complications
Seminoma	I	56	50	3
	II	17	10	2
	III	2	0	0
Non seminoma	I	47	32	6
	II	13	5	1
	III	16	1	0
Other tumors	I	3	1	0
	II	1	0	0
	III	1	0	0
Total		*156*	*99*	12

irradiation of the cervicothoracic spine (BODEN PALLIS et coll ATKINS & TR[illegible] 1966 PHILLIPS & BUSCHKE 1969 PALMER) Only a few authors (MAIER et coll MAIER 1972) have estimated the dose related risk of neurologic complications after irradiation of the lumbosacral spinal cord In order to assess the frequency of such complications in relation to the radiation dose administered a systematic clinical follow up was therefore undertaken of all patients still alive at least 2 years after irradiation of the lumbosacral cord for a malignant testicular tumor

Material and Treatment Method

The material consisted of all patients with malignant testicular tumors treated at this Department between February 1965 and October 1974 The period was chosen *to ensure that all patients had survived for at least 2 years after completion of therapy* Of the total material of 156 patients 99 were alive at the follow up in October 1976 Ninety five patients were examined clinically from the aspect of recurrences and neurologic complications Four who did not come to the follow up reported that they felt quite well and had no neurologic symptoms from the legs The material was distributed according to the microscopic appearance and to the clinical staging which followed the method employed at the Walter Reed General Hospital (Table 1).

The median age was 39 years (range 18–81 years) for patients with seminoma and 28 years (range 5–71) for the non seminoma group

The treatment of malignant testicular tumors was uniform throughout the period covered by the investigation After an ordinary orchidectomy irradiation was given either as a therapeutic measure to established lymph node metastases or as a pro-

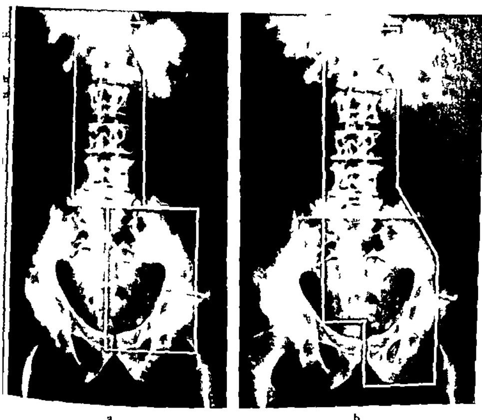


Fig 1 Arrangement of iliac and para aortic fields with 2 opposing anteroposterior fields for irradiation of malignant testicular tumors a) with Co b) with linear accelerator

phylactic to regional lymph nodes without known metastases Bilateral lymphography from the foot was used in nearly all the patients Biopsy of retroperitoneal lymph nodes was carried out in a few cases when metastases had been suggested at lymphography None of the patients had undergone retroperitoneal aortic lymphadenodectomy

The radiation fields included inguinal and iliac lymph nodes on the homolateral side and the para aortic lymph nodes bilaterally The commonly used treatment field appears in Fig 1 Its upper border was usually placed at the lower margin of the eleventh thoracic vertebra Only in 6 of the patients followed up were the mediastinal and supraclavicular nodes also irradiated because of metastases All the fields were adjusted under fluoroscopy with due consideration paid to lymphographic and urographic findings

Of the total material of 156 patients 57 (28 seminomas and 29 non seminomas) received cobolt teletherapy and 80 (46 seminomas 31 non seminomas and 3 other tumor forms) were irradiated with a 6 MeV linear accelerator Nineteen patients

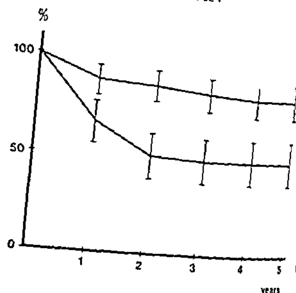


Fig 2 Actuarial survival curves for 75 patients with seminoma (upper curve) and 76 non seminoma patients (lower curve)

either because of age or widespread metastases were given no irradiation or only palliative pain killing treatment With cobolt teletherapy the fields must be divided into two due to the field length The radiation was given daily from the front and the back alternately Five patients were irradiated with a vertical beam and 5? with oblique beam in order to avoid overdosage (a hot spot) when the fields bordered on one another Irradiation with the linear accelerator was directed through one anterior and one posterior field Seventy three patients were irradiated daily through both fields 5 through one field daily and 2 with other fractionation schedules No correction for missing tissue was made in connection with the irradiation

During the period under review the central radiation dose and thereby also the dose to the spinal canal was 33 to 40 Gy/3 to 4 weeks for the seminomas and 40 to 57 Gy/4 to 6 weeks for the non seminomas with daily irradiations 5 to 6 times a week This means that the CRE values (the cumulative radiation effect) ranged from 1 000 to 1 450 reu (radiation effect units) for the seminomas and from 14?0 to 1 900 reu for the non seminomas

Results

Ninety nine of the 156 patients were alive at the time of the follow up The survival time for the material was calculated according to the actuarial method and the cumulative survival rates for the 75 patients with seminoma and the 76 non seminomas appear in Fig 2 The cumulative 5 year survival for the seminomas was 82 per cent (73–91 %, 95 % confidence limits) and for the non seminomas 49 per cent (38-6? %, 95 % confidence limits) According to the survival curves nearly all the deaths occurred within the first two years after the irradiation The observation time for patients alive at the time of the follow up was 2 to 12 years average 5 9 years Only

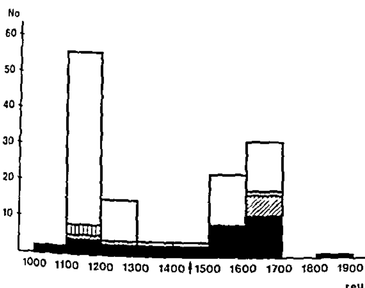


Fig 3 Distribution of the whole material according to the radiation dose (reu) Patients dead at time of follow up (black areas) alive without symptoms (white areas) with persisting neurologic symptoms (oblique shading) and with transient neurologic symptoms (vertical shading)

One of the patients in the follow up had signs of a recurrence of the testicular tumor 3 years after completion of radiation therapy He had no neurologic symptoms

Among the surviving 99 patients neurologic symptoms were present in 12 (12 %) None of those without subjective symptoms had objective signs of neurologic deficits

On the basis of the neurologic signs and symptoms present at the follow up a number of clinical syndromes could be distinguished (Table 2) Five patients (5 % Cases 1 5) had purely subjective mild discomfort in the form of paresthesias (4 instances) or a sensation of muscular weakness (1 instance) These symptoms disappeared after 3 to 6 months In 2 patients (2 Cases 6 and 7) the neurologic symptoms and signs were concentrated to the femoral nerve on the irradiated side they were persistent but caused little discomfort In 5 patients (5) the symptoms were considerable causing disablement of varying degrees 2 of them (Cases 8 and 9) had diffuse atrophy and paresis in one leg which in one instance necessitated a change of occupation from manual to office work and 3 (Cases 10–12) had severe symptoms with marked diffuse symmetric flaccid paresis in both legs affecting especially the gluteal muscles and the foot and toe extensors and causing a waddling gait and drop foot Only one of them (Case 12) had mild sensory symptoms in the form of hypoesthesia The deep reflexes in the legs in these 3 patients were markedly weak or absent but the plantar abdominal and cremasteric reflexes were normal No signs of bladder and rectum dysfunction or impotence were observed Myelography revealed arachnoiditis distal to the second lumbar vertebra in Case 10 but in Case 12 the arachnoid was normal In Case 11 myelography was not performed as the pa

Table 2

Survey of radiation treatment and clinical findings in 12 patients with neurologic complications

Case No	Age (years)	Latent period (months)	CRE (reu)	Neurologic symptoms and signs	Clinical course	Observation time after irradiation (years)
1	30	3	1 670	Paresthesia both feet	Disappeared after 3 months	3½
2	38	2	1 182	Painful paresthesia L leg	Disappeared after 3 months	5
3	30	2	1 146	Paresthesia both ankles	Disappeared after 6 months	8½
4	34	4	1 158	Paresthesia both legs	Disappeared after 6 months	7
5	42	9	1 250	Slight subjective weakness L leg	Disappeared after 6 months	3
6	34	5	1 670	Slight weakness R quadriceps Hypoesthesia ant aspect R femur	Unchanged	2½
7	52	6	1 149	Hypoesthesia ant aspect L femur and inside of L crus	Unchanged	3½
8	31	23	1 670	Moderate atrophy and paresis R leg Deep reflexes R. leg reduced	Unchanged	4
9	35	26	1 670	Moderate atrophy and flaccid paresis R leg Slight hypo esthesia inside R crus R foot drop	Unchanged	6
10	33	12	1 670	Severe atrophy and flaccid paresis of the gluteal femoral and ant tibial muscles Bilat foot drop Waddling gait	Unchanged	[illegible]
11	24	10	1 670	Marked bilat atrophy and paresis of gluteal muscles peroneal reflexes absent Waddling gait	Gradual improvement	4½
12	25	14	1 608	Severe atrophy and paresis of both legs Slight hypoesthesia R ankle Able to walk with crutches	Gradual worsening 5 years after onset of symptoms	8½

tient's symptoms had been receding over the past year, in that he had been able to discard his crutches. The symptoms had remained unchanged in Case 10, whereas in Case 12 they had become worse, being most severe 5 years after onset.

One of the patients who died had 2 months after the irradiation developed moderate paraparesis which remained unchanged until he died one year later from peritonitis resulting from radiation necrosis of the colon. At autopsy no signs of tumor recurrence but marked fibrosis in the small pelvis were observed. This patient was not included among the cases with complications as the spinal cord was not examined at autopsy and the possibility of metastases to the cord could therefore not be excluded. None of the other patients who had died developed neurologic deficits.

The latent period between completion of irradiation and the first neurologic symptoms was shorter, 2 to 9 months (average 4 months), in the group (Cases 1–5) with purely subjective and transient symptoms than in the group with persisting symptoms in which it ranged from 5 to 26 months (average 14 months).

The irradiation of the above 12 patients with neurologic symptoms did not deviate from the standard procedures. Three patients received cobolt teletherapy through an led a p fi lds, one was treated with a linear accelerator through one field daily and 8 with a linear accelerator through anterior and posterior fields daily. None of the patients with neurologic symptoms had received chemotherapy.

The relation between the radiation dose given and the degree of the neurologic symptoms appears in Fig. 2. There was a close connection between the severity of the symptoms and the dose, all patients with persisting pareses having received more than 1 600 reu. Only one patient with persisting symptoms, which however were purely sensory, had received a dose below this level. Of the 33 patients who received more than 1 600 reu, 20 were alive at the time of the follow up, among these 3 had paraparesis causing considerable walking difficulties and 2 paresis in one leg preventing heavy physical work.

In order to assess the significance of the length of the irradiated field the number of patients with paresis in the group with lengths shorter than 36 cm (2 among 43 cases) was compared with the number in the group with lengths of 36 cm or longer (4 of 50 cases). No significant difference was established (Fisher's exact text, $p = 0.43$).

Discussion

The neurologic complications after irradiation could in this series be divided into three groups. One group comprised 5 patients with purely subjective mild symptoms of the type described by JONES. None of these patients had Lhermitte's sign, however. In the second group, with 2 patients, the symptoms could be ascribed to an isolated injury to the femoral nerve, as described by SPIESS. In accordance with SUNDERLAND's (1972) description, the symptoms in these patients with femoral neuropathy were mainly sensory. They were constant, but not incapacitating.

In a third group, comprising 5 patients, the symptoms were consistent with the

clinical findings in the post irradiation neuropathy reported by GREENFIELD & STARK but none of the patients had fasciculation and the paresis was unilateral in 2 cases A remarkable feature was that no bladder rectum or sphincter disturbance or definite sensory loss existed in any of the cases The pareses were especially marked in the gluteal muscles and in the extensors of the foot which resulted in a characteristic rolling gait and drop foot

The neurologic signs of a persisting neuronal lesion following irradiation usually develop after a latent period in the present series this was 14 months on an average (range 5–26 months) Latent periods of up to 13 years have been mentioned in the literature although a period longer than 2 years has been reported for only 6 out of 64 cases (PALLIS et coll KRISTENSSON et coll 1967 REAGAN et coll SOLHEIM 1971 BURNS et coll 1972 PALMER GODWIN AUSTEN et coll 1975)

In most of the present patients with persisting lesions the symptoms remained unchanged but in one case the pareses worsened appreciably 5 years after onset and in another an improvement took place 2 years after onset Such an improvement is rare but has been reported by SOLHEIM

A number of factors are of significance in the definition of an irradiation treatment and an assessment of the possible injury to nerve tissue arising from this therapy Thus the following factors must be taken into consideration total dose dose per fraction number of fractions total treatment time and field size In most of the previous investigations to determine the connection between radiation dose and neurologic complications dose time curves have been compiled based on regression lines for the tumor dose in Gy/treatment time in patients who developed symptoms (BODEN PALLIS et coll MAIER et coll) or the tumor dose in Gy/number of fractions (ATKINS & TRETTER) both for short and for long fields With these methods only a few of the significant factors are included ELLIS (1967 1969) introduced the NSD value (nominal standard dose) which includes all the above mentioned factors except field size PHILLIPS & BUSCHKE used the NSD value when assessing the risk of radiation myelitis in the thoracic part of the spinal cord and suggested a tolerance limit at 1 500 ret (radiation equivalent therapy) MAIER established a mean dose of 1 366 ret among 15 patients who developed myelitis after irradiation of malignant testicular tumors and suggested a tolerance limit at 1 300 ret

KIRK et coll (1971) reworked Ellis s formula for the NSD introducing instead the CRE value (cumulative radiation effect) to solve the problems connected with the concept of partial tolerance These problems arise in connection with alteration of the fractionation or gaps during therapy The NSD value is directly comparable to the CRE values in the present series if the fractionation was constant throughout the treatment period and no gaps existed If intervals of more than 4 days occurred in the present series a correction was made for the effect of the gaps on the CRE value (TURESSON & NOTTER) No signs of appreciable neurologic complications were observed in patients who had received less than 1 600 reu On the other hand 5 of 20 survivors given a dose of more than 1 600 reu had neurologic complications 3 of

these (15 %) had severe disabling paraparesis and 2 (10 %) moderately severe disabling paresis in one leg Thus the findings indicate that the tolerance limit for the spinal cord at the lumbar level lies at a value of not over 1 600 reu which means a dose of 54 5 Gy over a period of 6 weeks with daily fractions 5 times a week

Acknowledgement

Thanks are due to Mr J Munk for technical assistance with the calculation of the radiation doses

SUMMARY

Of 156 consecutive patients with malignant tumor of the testis 99 were alive two years after treatment Of these 12 had radiation induced neurologic complications which in 5 instances consisted of persisting wholly or partially disabling paresis in the lower limbs Five had mild transient symptoms and 2 had persisting symptoms which were not incapacitating In all those with disabling symptoms the irradiation dose had been higher than 1 600 reu corresponding to 54 5 Gy over 6 weeks with daily fractions 5 days a week

ZUSAMMENFASSUNG

Zwei Jahre nach der Therapie waren 99 von 156 konsekutiven Patienten mit malignen Tumoren des Testis am Leben Von diesen hatten 12 strahlenbedingte neurologische Komplikationen welche in 5 Fallen aus totaler oder partieller invalidisierender Lahmung der unteren Extremitaten bestand Funf hatten lediglich subjektive geringe voruber gehende Symptome und 2 hatten bestehende doch nicht invalidisierende Symptome Bei denjenigen welche invalidisierende Beschwerden hatten war die Strahlendosis hoher als 1 600 reu entsprechend 54 5 Gy in 6 Wochen mit taglichen Fraktionen 5 Tage pro Woche

RESUME

Quatre vingt dix neuf malades sur une serie consecutive de 156 cas de tumeur maligne du testicule étaient en vie 2 ans après le traitement Parmi eux 12 avaient des complications neurologiques dues aux radiations qui dans 5 cas consistaient en une parésie des membres inférieurs complètement ou partiellement invalidante Cinq n avaient que des symptomes purement subjectifs légers et transitoires et deux avaient des signes fonctionnels ne causant pas d inconfort Chez tous les malades atteints de troubles invalidants la dose d irradiation avait été superieure à 1 600 reu correspondant a 54 5 Gy en 6 semaines avec des doses journalières 5 jours par semaine

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FROM THE INSTITUTE OF MEDICAL RADIOBIOLOGY KAROLINSKA INSTITUT
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SECRETION OF $^{99}Tc^{m}$ IN BREAST MILK AFT INTRAVENOUS INJECTION OF MARKED MACROAGGREGATED ALBUMIN

B TRIBUKAIT and G A SWEDJEMARK

The administration of radiopharmaceuticals to women during lactation involves a risk that a breast feeding child may be exposed to radiation due to activity secreted in the milk

In a recent case the question arose as to whether a nursing mother who was subjected to a lung scan with technetium marked albumin should interrupt breast feeding to her 3 month old child and if so for how long

The 26-year old patient was referred for a lung scan because of possible lung embolism The patient received approximately 74 MBq (2 mCi) of $^{99}Tc^{m}$ macroaggregated albumin intravenously She was advised to interrupt breast feeding and she was requested to pump out milk at the times when feeding normally took place and to send milk samples for analysis

Methods

The $^{99}Tc^{m}$ activity was measured in a NaI (Tl) 3 × 3 (7 62 × 7 62 cm) well crystal connected to a multi channel analyser The calibration constant used had been obtained with a previous calibration with a $^{99}Tc^{m}$ solution The smallest detectable quantity 3σ above background was 90 Bq/10 ml (2 4 pCi/10 ml) for a measurement

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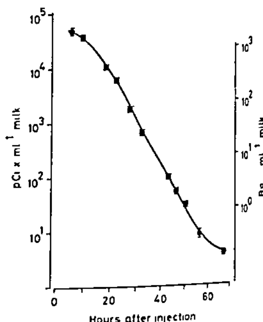


Fig 1 $^{99}Tc^m$ concentration in breast milk expressed in mCi/ml and Bq/ml of milk 5 5–67 5 h after intravenous injection of approximately 74 MBq (2 mCi) of $^{99}Tc^m$ macroaggregated albumin The errors in the counting statistics and the uncertainties in the time specifications have been given (±1 σ)

Results

The results of the measurements of the $^{99}Tc^m$ concentration in 11 milk samples taken between 6 and 68 h after the injection appear in Fig 1 Apart from some deviations at the beginning and end of the observation period the concentration diminished almost exponentially with an effective half life of 4 hours The physical half life of 6 was therefore the dominant effect

The measurement values corrected for the physical decay and expressed as fractions of the administered activity show this deviation clearly (Fig 2) With this presentation the maximum technetium concentration in the milk is found 15 h after the $^{99}Tc^m$ injection Towards the end of the observation period the rate of secretion levels out The results show the biologic half life to be approximately 10 h

Discussion and Conclusions

Reports in recent years have appeared on the secretion of activity in breast milk after the administration of $^{99}Tc^m$ to a nursing mother (VAGENAKIS et coll 1971 BERKE et coll 1973 WYBURN 1973 CARMODY & HIGHMAN 1975 O CONNELL & SUTTON 1976) However only one of these reports (BERKE et coll) deals with the $^{99}Tc^m$ macroaggregated albumin which was used in this case That report also refers to whole body measurements of five children after injection of $^{99}Tc^m$ for brain scanning resulting in an estimated whole body dose of 22 μGy/MBq (0 81 mrad/μCi) to a 6-month old child According to HINE & JOHNSON (1970) the corresponding value for adults is 3–5 μGy/MBq (0 01–0 02 mrad/μCi) On the basis of these values the radiation dose to the 3 month old child has been estimated to be 43 μGy/MBq (0 16 mrad/μCi) (1 mCi = 37 MBq 1 mrad = 0 01 mGy = 10 μGy 1 mrad/μCi ≈ 2.70

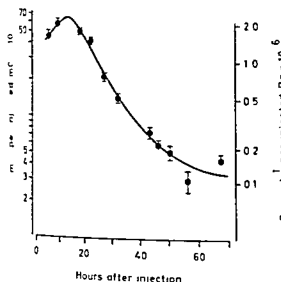


Fig 2 ^{99}Tc^{m} concentration in breast milk related to the injected activity corrected for the physical decay 5 5 to 67 5 h after injection The errors have been shown $\pm 1\sigma$ for the uncertainty in the counting statistics and for the uncertainty in the time specifications for the injection and sampling

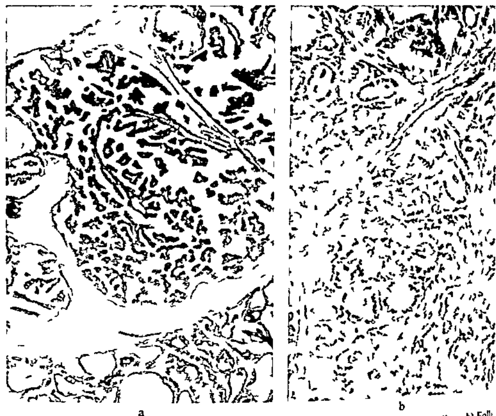
μGy MBq) If the child had drunk 150 ml milk/meal it would have accumulated a whole body dose from the milk varying from 26–0 001 μGy (2 6–0 0001 mrad) (Table) if breast feeding had been resumed at the various times during the observation period shown in the Table In addition the child is exposed to external radiation from the mother This dose is comparable to that obtained from the milk

The magnitude of the radiation dose is so small that the risk to the child can be regarded as negligible even if the mother had continued breast feeding immediately after the lung scan In the present case the mother resumed breast feeding 24 hours after the lung scan

Table

Estimated absorbed dose in the child from breast milk

Hours	Cumulative absorbed dose in total body of the child	
	μGy	mrad
If feeding begun		
5 5 after injection	26	2 6
9 5	14	1 4
18 5 "	5 0	0 50
22.5 "	2 2	0 22
27.5	0 64	0 064
37 5	0 20	0 020
43 5	0 048	0 0048
46 5 "	0 024	0 0024
50 5 "	0 010	0 0010
56 5 "	0 004	0 0004
67 5 "	0 001	0 0001



Adenocarcinoma of the thyroid induced by irradiation for Hodgkin s disease a) Papillary b) Follicular

Discussion

The relationship between irradiation and thyroid carcinoma is controversial Many authors have reported thyroid carcinoma following irradiation of the thyroid gland during childhood (DUFFY & FITZGERALD 1950 CLARK 1955 SIMPSON et coll 1955 DE GROOT & PALOYAN 1973 PARKER et coll 1974) On the other hand such a development has been denied by SNEGIREFF (1959) BEREGI et coll (1967) and SIMIONESCU (1970) In the literature only 3 cases have been reported in whom thyroid carcinoma has developed following irradiation of malignant lymphoma RAVENTOS & WINSHIP (1964) described 2 cases and FUKS et coll (1976) one case of Hodgkin s disease who developed a thyroid carcinoma of the papillary and follicular type 9 years after irradiation of the neck including the thyroid gland with a dose of 33 Gy

During the past 30 years 207 patients with Hodgkin s disease have been irradiated to the neck in this department including the thyroid gland 8 2 per cent being under the age of 11 years The only one who developed malignancy in the thyroid gland is the present case

The irradiation doses which are considered to produce thyroid carcinoma range between 0 5 and 15 Gy Most children who developed thyroid carcinoma had received 2 Gy to the thymic area (SNEGIREFF)

LATOURETE & HODGES (1959) found thyroid carcinoma in 1 5 per cent of the cases given 3 5 to 5 Gy Even a dose of 0 01 Gy to this region increases the carcinoma morbidity from 0 5 (SOKAL 1954) to 1 5 per 100 000 (PARKER et coll)

The latent period until the appearance of a thyroid tumor, ranges between 3 months and 37 years (WILSON et coll 1970) This latency depends on the age of the patient at irradiation (DE GROOT & PALOYAN) It is shorter when the irradiation is given between 3 and 6 years longer between 11 and 13 Above 13 years of age it is shorter again In females it is shorter than in males (HEMPELMANN et coll 1975) The average latent period is 10 9 years and is proportional to the dose (RAVENTOS & WINSHIP)

At microscopy most of the tumors of the thyroid induced by irradiation are papillary and follicular adenocarcinoma with sclerotic components (PARKER et coll BOURDIAL et coll 1970) They are multifocal and usually bilateral (WILSON et coll) Different stages of development from benign adenoma to papillary and follicular adenocarcinoma may be encountered

It may be assumed that the thyroid carcinoma in the present case was due to the neck irradiation for Hodgkin s disease This assumption is based upon the fact that the tumor appeared during the expected time of latency and that the tumor was bilateral and multifocal intermediate stages between adenoma and papillary and follicular adenocarcinoma which are typical to radiation induced carcinoma were present

At the present time irradiation is one of the most important types of treatment of Hodgkin s disease and 13 1 per cent of the patients are under 14 years of age (O CONNOR et coll 1972) Because of the good prognosis of the disease it may thus be expected that the incidence of radiation induced thyroid carcinoma will increase

SUMMARY

In a 22 year-old male who had been irradiated 16 years previously for Hodgkin s disease a radiation induced thyroid carcinoma developed This was the only case with such development in a group of 207 cases with Hodgkin s disease who were treated by irradiation including the thyroid gland

ZUSAMMENFASSUNG

Bei einem 22 Jahre alten männlichen Patienten der 16 Jahre vorher wegen einer Hodgkinscher Erkrankung bestrahlt worden war entwickelte sich ein Strahleninduziertes Thyreoidea Karzinom Dieser war der einzigste Fall bei dem sich in einer Gruppe von 207 Fällen mit Hodgkinscher Erkrankung die durch Bestrahlung einschliesslich der Thyreoidea behandelt worden waren ein Karzinom entwickelte

RESUME

Un carcinome thyroïdien induit par les radiations est apparu chez un homme de 22 ans qui avait été irradié 16 ans auparavant pour une maladie de Hodgkin C est le seul cas avec cette complication dans un groupe de 207 cas de maladie de Hodgkin traités par irradiation incluant la glande thyroide

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FROM THE DEPARTMENT OF RADIATION THERAPY (DIRECTOR I GYNNING) MALMÖ ALLMÄNNA SJUKHUS S 14 01 MALMÖ SWEDEN

HIGH DOSE MEDROXYPROGESTERONE-ACETATE TREATMENT IN ADVANCED MAMMARY CARCINOMA

A phase II investigation

W MATTSSON

Since BEATSON (1896) introduced oophorectomy hormonal treatment has until recently been the main mode of therapy of metastatic mammary carcinoma In unselected material remissions have been obtained in 20 to 35 per cent of patients treated with ablative hormonal surgery (CARBONE 1977 GRATTAROLA 1976 MECKLENBURG & LIPSETT 1975 NEWSOME et coll 1977 PUGA et coll 1976 SEGALOFF 1975 SILVERSTEIN et coll 1975 YONEMOTO et coll 1977) as well as with additive hormonal treatment with androgens oestrogens progestins and corticosteroids (ANSFIELD et coll 1974 CARTER et coll 1977 GOLDENBERG et coll 1973 KENNEDY 1974 MUGGIA et coll 1968 NISSEN MEYER & VOGT 1959 SEGALOFF) and antioestrogens (LEGHA & CARTER 1976 LEGHA et coll 1976 TAGNON 1977 WARD 1973) The finding of hormonal receptors in mammary carcinoma and their predictive usefulness in hormonal treatment (JENSEN et coll 1971 LECLERCQ & HEUSON 1977 MCGUIRE 1973 MCGUIRE et coll 1975) has revived interest in hormonal therapy particularly with antioestrogen The antioestrogens Tamoxifen Nafoxidine and Clomiphene have an objective effect in 50 per cent or more of all cases of oestrogen receptor positive metastatic disease (BARNES et coll 1977 LECLERCQ & HEUSON MCGUIRE et coll MORGAN et coll 1976 MOURIDSEN et coll 1977) like other forms of hormonal treatment (LEGHA & CARTER)

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Progestin may act as antioestrogen both directly on tumor cells by inhibiting binding of oestradiol to receptors (GURPIDE 1976) and indirectly by reducing the amount of oestrogen available to the tumor cells by increasing the catabolism of oestrogen decreasing the conversion of androgen to oestrogen and by medical suppression of hypophyseal release of LH and FSH (GURPIDE, HELLMAN et coll 1976 MASCIA et coll 1977) Furthermore progesterone receptors may perhaps be inhibited by progestin

Previously progestin in metastatic breast carcinoma has been reported to give a response rate of 10 to 35 per cent after small and intermediate doses (50 to 400 mg) of medroxyprogesterone (MAP) (ANSFIELD et coll GOLDENBERG 1969 MUGGIA et coll SEGALOFF et coll 1967, SEGALOFF, STOLL 1967) Higher rates of remission have been found in patients treated with a high dosage of MAP <1 000 mg day (PANNUTI et coll 1975, 1976, AMADORI et coll 1976) These clinical results and biologic actions of progestin motivated the use in this department of high dosage MAP in very advanced breast carcinoma The main purpose was to assess the clinical effect and the tolerance of patients who had previously been treated with different kinds of hormones or combination chemotherapy

Material and Methods

The criteria for inclusion in the material consisting of 25 patients were measurable lesions Karnofsky s performance index >30 points (KARNOFSKY & BURCHENAL 1949) relapses after other endocrine treatment or resistance to combination chemotherapy All patients were postmenopausal either naturally or artificially a d all were evaluable The median age was 69 years (range 34 to 94 years) Seventeen patients were 60 to 79 years old In 22 patients the primary therapy had been modified radical mastectomy followed by postoperative irradiation of the regional lymph nodes and operation fields Two patients had received irradiation of their primary inoperable tumors One patient had not been treated by any local therapy The first median relapse free interval was 18 months (0 to 110 months) The median time between the diagnosis of a relapse or a metastasis and MAP therapy was 20 months (range 0 to 64 months)

Previous treatment of metastases In 23 patients several modalities of treatment for metastases had been tried (Table 1) The median number of previous courses was 3 (range 0 to 5) Only 2 patients received MAP as the primary treatment of metastases as they were scored 40 points according to Karnofsky s index indicating poor tolerance to combination chemotherapy which otherwise should have been the treatment modality

The previous hormonal treatment had consisted of oophorectomy (9 patients) andogrens (10 patients) oestrogens (3 patients) and corticosteroids (2 patients) These therapeutic measures had resulted in 5 partial remissions and no changes in 4

Table 1

Previous therapy of metastases

Hormonal treatment	
Oophorectomy	9
Androgen	10
Oestrogen	3
Corticosteroid	2
Tamoxifen	20
Cytotoxic chemotherapy	
CMFP (Canellos et coll)	6
VACM (Mattsson et coll)	12
Radiation therapy	11
Surgery	
Osteosynthesis	4
Tracheostomy	1
Extended cutaneous excision	1
No previous treatment	2

In 5 of 20 patients previously treated with Tamoxifen 30 mg a day a partial remission with a median duration of 6 months (range 3 to 11 months) was obtained Before MAP treatment 15 of 18 patients had had a remission (median duration 12 months) in association with combination chemotherapy with either Vincristine Adriamycin Cyclophosphamide and Methotrexate with citrovorum factor rescue (MATTSSON et coll 1977 a b) or Cyclophosphamide Methotrexate 5-Fluorouracil and Prednisone (CANELLOS et coll 1974)

Eleven patients had been subjected to local palliative irradiation of the skeleton (14 Gy)

Examinations before the MAP therapy was started the extent of the disease was assessed by clinical and gynecologic examination chest and skeletal radiography isotope scanning of the liver and fine needle aspiration biopsy of accessible metastases in the skin lymph nodes lungs and liver When clinically indicated these examinations were supplemented by mammary radiography urography ultrasonic examination of the abdominal and pelvic cavity and isotope scanning of the brain and of the skeleton Laboratory examinations included determination of haemoglobin erythrocytes leukocytes differential counts platelets serum iron total iron binding capacity electrolytic status creatinine and liver function Electrophoresis ECG microscopy of the urinary sediment and CEA were also performed The patients symptoms were recorded according to Karnofsky s performance scale

Spread of metastases and performance state The median number of organs with metastases was 3 (range 1 to 6) The dominant site was in soft tissues in one patient

Table 2

Results of MAP therapy

	No of patients	Duration of remission		Alive in remission	Alive with a relapse
		Median	Range		
Partial remission	7	5+	(2+–13+)	5	1
No change	7	4	(3–6)	3	1
Progressive disease	11				

in the skeleton in 3 and in the viscera in 21 The most common tissue involved was bone (21 patients) The other metastatic sites were the lungs in 12 pleurae liver and lymph nodes in each of 9 the skin in 6 and the breast in 3 patients Other less common sites were the brain peritoneum mediastinum bowel ovaries and uterus The median Karnofsky s performance index was 60 points (range 40 to 80)

Treatment and follow up The patients were treated with medroxyprogesterone acetate (MAP Farlutal Farmitalia) intramuscularly in the buttocks in a dose of 1 000 mg a day for 30 days The patients who had then obtained a remission (≥no change) by this induction regimen of MAP (30 g) continued to take a maintenance dose of 1 000 mg a week until progressive disease was detected

The effect was estimated every other week for 12 weeks by means of physical examination assessment of Karnofsky s performance index and determination of the haemoglobin leukocytes differential count liver function creatinine electrolytic status Chest and skeletal radiography and isotope scans of the liver were obtained at least once every 4 weeks Other examinations performed to document the remission were ultrasonic examination of the abdominal and pelvic cavity isotope scanning of the brain and mammary radiography

After the first 12 weeks of treatment the follow up was individualized but at intervals of at most three months remissions were evaluated and the Karnofsky s performance index of the patients was assessed After 6 and 12 months treatment the pretreatment examinations were repeated in all survivors Of the 12 patients who died 11 were examined post mortem

Assessment of response The criteria used for remissions were those recommended by HAYWARD et coll (1977) Complete remission is a disappearance of all known disease In cases with lytic bone metastases radiography must have shown that the lesions have calcified Partial remission is a decrease of 50 per cent or more in measurable lesions and objective improvement of evaluable but non measurable lesions and no new lesions No change is recorded when the size of measurable lesions decreases less than 50 per cent or increases less than 25 per cent Progressive disease is recorded when some lesions regress while others progress or new lesions appear or when some or all lesions progress or new lesions appear

Table 3

Results of MAP therapy in relation to dominant metastatic organ

Organ	Partial remission	No change	Progressive disease
Soft tissue	—	1	—
Bone	2	—	1
Visceral	5	6	10
Total	7	7	11

Results

The overall response rate was 28 per cent (partial remission in 7/25 Table 2) To date (1 February 1978) the median duration of these partial responders is 5 months (range 2– to 13– months) Five of these patients are alive in remission and one with a relapse now responding to combination chemotherapy The one responder who had died had a remission for 5 months Seven patients had no change for a median duration of 4 months (range 3 to 6 months) Three of them are still alive without signs of tumor progression and one with a relapse which has become stationary during combination chemotherapy The other 3 patients with no change died after 3 6 and 8 months respectively Combination chemotherapy was tried but no response was obtained The 11 non responders had a median survival of 4 months (range 0 5 to 9 months) Two of them are still alive and respond to combination chemotherapy Three of the patients with progressive disease did not respond to subsequent combination chemotherapy Five non responders did not receive any treatment when the disease progressed because of lesions which were too extensive

In 2 out of 3 patients with dominant bone metastases and in 5 out of 21 with visceral metastases a remission occurred (Table 3) The response did not vary significantly with the number of metastatic organs involved although 2 out of 5 with one organ with metastases responded compared with 3 out of 10 patients with metastases in 4 or more organs (Table 4)

Previously 5 out of 21 patients had a remission in association with hormonal treatment other than Tamoxifen (Table 5) Three of these responders and one non responder had a remission by MAP therapy Before treatment with MAP 20 patients had also received Tamoxifen which resulted in partial remission in 5 patients When one of these responders relapsed she responded to MAP treatment Further more among the 15 Tamoxifen resistant patients MAP therapy resulted in 4 partial remissions and in no changes in 4 (Table 5)

Fifteen of 18 patients had previously had a remission during combination chemotherapy When they were later treated with MAP 4 of these 15 had a partial

Table 4

Results of MAP therapy in relation to number of metastatic organs

No of metastatic organs	Partial remission	No change	Progressive disease
1	2	1	2
2	1	2	—
3	1	3	3
≥4	3	1	6
Total	7	7	11

$0.5 < p < 0.7$ Kruskal Wallis log rank test

remission and 3 evidenced no change None of the 3 non responders to combination chemotherapy responded to MAP therapy (Table 5)

The subjective improvement of the partial responders as measured by Karnof ky's performance index was 10 to 40 points (median 20) The seven patients with no chan had a median improvement of 20 points (range 0 to 30) In no patient was MAP therapy followed by a decrease of performance On the contrary 4 of the 11 patient with a progressive disease improved subjectively with relief of pain increased appetite and better feeling of well being

The therapy was well tolerated Only 5 patients complained of some distention in the buttocks following the injections All but one patient had local infiltration a the site of injection In one patient a severe bleeding occurred probably due to a puncture of a muscle artery A necrotic ulcer developed which healed after plasti surgery No patient had any objective or subjective retention of wat r No renal gastrointestinal haematologic or gynecologic adverse effects occurred Three patient had transient moderate elevation of liver function Slight moon face as in Cushing disease occurred in 4 patients but no other adverse effects of adrenocorticoid coul be detected

Discussion

The overall rate of objective response (28 %) by high dosage MAP in thes patients with advanced disease who previously had been heavily treated with othe means is encouraging The results compare favourably with the rate of remissio obtained by other primary hormonal therapy in unselected metastatic breast carci noma (CARTER et coll GOLDENBERG et coll KENNEDY LEGHA & CARTER MECKLEN BURG & LIPSETT NOTTER 1975 PUGA et coll SEGALOFF SILVERSTEIN et coll TAG NON YONEMOTO et coll WARD WESTERBERG et coll 1976)

The response rate in the present material was lower than that reported b PANNUTI et coll (1975 1976) and AMADORI et coll This could be explained by th

Table 5

Results in relation to outcome of previous treatments of metastases

Results of previous therapy of metastases		Results of MAP		
		Partial remission	No change	Progressive disease
Hormonal therapy other than Tamoxifen				
Objective response	5	3	1	1
No change – progressive disease	16	1	3	12
Tamoxifen				
Objective response	5	1	1	3
No change – progressive disease	15	4	4	7
Combination chemotherapy				
Objective response	15	4	3	8
No change – progressive disease	3		1	2

disease being more advanced (median number of metastatic sites 3 dominant visceral metastases 21/25) and by the previous more extensive treatment (median number of previous treatments 3) KENNEDY has shown that the rate of remission following hormonal therapy is related to the extent of the tumor An established fact is that the chance of a new remission in patients not responding to other types of hormone therapy is less (HASKEL 1977) At any rate the response rate in these previously heavily treated patients is about the same as that followed by small and moderately large doses of MAP as the primary treatment of metastases (ANSFIELD et coll GOLDENBERG 1969 MUGGIA et coll SEGALOFF et coll STOLL)

The duration of remission seemed to be short in most of these advanced cases A possible explanation is that most tumors consist of both hormone-dependent and hormone independent cells (TAGNON 1976 WITTLIFF et coll 1976) Furthermore TAGNON (1977) has produced some evidence that hormone therapy might eradicate tumor cells with oestrogen receptors and together with KENNEDY s observation of the importance of the tumor burden there may be a better possibility of increasing hormone independence with increasing tumor volume and previous hormonal treatment, as in the present material

Long and uniform experience has shown that the chance of a remission following hormonal therapy in patients with visceral metastases particularly in the liver is poor The literature contains no conclusive data about the content of hormone receptors at different metastatic sites Available data on the rate of response in

various organs indicate that the hormone dependent tumor cells occur in the different organs in the following order soft tissue bone lung pleurae and then the other viscera Also other factors may be important such as the available therapeutic concentration of the drugs and the complex importance of different hormones to promote or suppress tumor growth (GURPIDE) At any rate in the present series MAP had an objectively demonstrated effect in 5 of 21 patients with dominant visceral metastases In addition in 6 patients the disease became stationary

Interesting both from theoretical and clinical points of view is the fact that there were 4 partial responders and 4 unchanged of 15 patients who had not responded to antioestrogen treatment Progesterone is considered to act both by inhibiting oestradiol binding to receptor protein in the cytoplasm of the tumor cells (HSUEH et coll 1975) and by the inhibition of the hypophyseal release of FSH LH and ACTH (GURPIDE GORDON et coll 1971) Furthermore progesterone depresses the level of oestradiol by enzymatically accelerated catabolism of oestrogen and secondary to increased catabolism of androgen reduces the conversion of androgen to oestrogen (GORDON et coll) With special regard to MAP TERENIUS (1974) has shown that MAP has a very high affinity for progesterone receptors in experimental animals MAP has also a direct anti proliferative effect as demonstrated by its inhibition of DNA and RNA synthesis (NORDQUIST 1970) and its reduction of mitotic index in adenocarcinoma of the endometrium (BINARD 1970) WILLIS et coll (1977) have shown that Tamoxifen invariably depresses the serum LH and FSH However in the non responders also oestradiol was increased The results of MAP in these non responders may be due to the progesterone mediated increased catabolism of oestradiol by which the oestradiol available to tumor cells was depressed Furthermore a competitive inhibition at receptor levels might have occurred

Although the number of patients is relatively small the results suggest no cross resistance between Tamoxifen and MAP Thus high dosage MAP can induce remission in Tamoxifen resistant patients since partial remission was obtained in 4 patients and no progression of the disease in 4 High dosage MAP could therefore be recommended to postmenopausal patients with metastases from breast carcinoma at least as a second line hormonal therapy particularly in elderly patients or in those in such poor condition that they do not tolerate combination chemotherapy

Previously 15 out of 18 patients in the present material had responded to combination chemotherapy All these patients had relapsed and were subsequently treated with MAP which resulted in partial remission in 4 and no change in 3 No adverse effect of previous cytotoxic chemotherapy was observed On the basis of the hypothesis that mammary carcinoma consists of both hormone dependent and hormone independent tumor cells an interesting approach is to combine high dosage MAP with cytotoxic drugs Promising results have already been obtained in two randomized investigations (MASCIA et coll STOTT et coll 1973) and in one non randomized controlled investigation (HUYS et coll 1976) Recently BRUNNER et coll (1977) in another randomized investigation did not find any advantage of adding

MAP to combination chemotherapy These 4 materials differed from each other in the dose of MAP and cytotoxic drugs used in the three with increased response rate the dose of MAP was 800 mg 1 000 mg and 4 200 mg a week respectively The dosage of MAP is of crucial importance PANNUTI et coll (1975) and AMADORI et coll have shown a dose response relationship ROBUSTELLI DELLA CUNA et coll (1978) found the same response rate to 500 mg MAP a day and 1 000 mg a day (44 versus 41) Therefore the most appropriate dose seems to be ~500 mg a day as a dose of 50 to 400 mg gave a response rate of 9 to 30 per cent (ANSFIELD et coll GOLDENBERG WIGGINS et coll PANNUTI et coll 1975 STOLL)

In the material of MASCIA et coll the determinations of serum FSH LH and prolactine were made prospectively Patients treated with combined chemotherapy and MAP (600 mg a day) had significantly lower FSH and LH than the group that received chemotherapy only These findings might help to explain the better effect of the combined therapy and lend support to the suggested dosage (> 500 mg a day) necessary to inhibit the hypophyseal release of FSH and LH

The present results did not vary significantly with the number of metastatic organs involved, a finding contrasting with what was stated in a previous report of combination chemotherapy in breast carcinoma metastases (MATTSSON et coll 1977 a) This may be explained by the different actions of cytotoxic drugs The effect of chemotherapy depends primarily on the growth fraction which varies approximately inversely with the tumor burden Some preliminary data suggest a larger content of glucolytic enzymes in tumors responding to cytotoxics (SAVLOV et coll 1977) On the other hand a low level of glucolytic enzymes was associated with the presence of oestrogen receptors (HILF et coll 1973) Another observation indicates that a primary tumor with a large growth fraction as measured by a high thymidine labelling index tends to recur early and probably contains a low incidence of oestrogen receptor (MEYER et coll 1977)

High dosage MAP was well tolerated Only one severe complication occurred it was probably related to accidental puncture of a muscle artery In no other case was aseptic necrotic ulceration observed This is in contrast with the results reported by PANNUTI et coll (1976) Aseptic necrotic ulcerating has been attributed to the use of MAP in soluble form However as the present patients received a median dose of 70 g (range 30 to 108 g) without that type of adverse effect it seems probable that previously described aseptic ulcerations were not due to the solution of MAP in se but to needle punctures of arteries or too high pressure in the muscle tissue at the site of injection A necrotic aseptic ulcer might occur secondary to bleeding and muscular injury

Measured by Karnofsky s performance index the median improvement was 20 points (range 0 to 40 points) Furthermore in 4 cases of progressive disease the quality of life improved The most important subjective benefits were increased appetite better feeling of well being and reduction of pain MARTINO & VENTAFRIDDA (1976) have analysed MAP for its analgesic efficacy in women with advanced breast

carcinoma and severe chronic pain not controllable with conventional analgesics

They found high dosage MAP to give substantial relief, which was in part due to the euphoric effect of the steroid

In conclusion high dosage MAP has produced promising results without any noteworthy adverse effects in very advanced and heavily pretreated patients with breast carcinoma metastases although the duration of the remissions was short. Particularly interesting is the effect on Tamoxifen resistant metastatic disease which suggests another mode of action besides the direct effect on tumor cells Previous combination chemotherapy and hormonal treatment did not have any adverse effect on the rate of remissions Randomized investigations comparing high dosage MAP with Tamoxifen in receptor positive metastatic disease and relapses after combination chemotherapy have been activated Thus it appears that MAP implies a new possibility of treating advanced mammary carcinoma

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SUMMARY

In a phase II investigation of high dose medroxyprogesterone treatment of advanced and previously with other methods heavily treated patients with mammary carcinoma 7 of 25 patients had a partial remission with a median duration of 5 + months In a further 7 patients the disease became stationary As measured by Karnofsky s scale a median improvement of 20 points was obtained in these 14 patients In 4 of 15 patients who had not responded to Tamoxifen treatment a partial remission occurred following MAP therapy The patients tolerated MAP well

ZUSAMMENFASSUNG

In einer Phase II Untersuchung über die Medroxyprogesterone Behandlung in hoher Dosierung bei vorgeschrittenen und zuvor mit anderen Methoden hochbehandelten Patienten mit Mamma Karzinom hatten 7 von 25 Patienten eine partielle Remission mit einer mittleren Dauer von 5 Monaten Bei weiteren 7 Patienten wurde die Erkrankung stationär Gemessen mit der Karnofskyschen Skala wurde eine mediane Verbesserung von 20 Punkten bei diesen 14 Patienten erreicht Bei 4 von 15 Patienten die nicht nach Tamoxifen Behandlung verbessert wurden wurde eine partielle Remission nach MAP Therapie erzielt Die Patienten vertrugen MAP gut

RÉSUMÉ

Dans une phase II d une recherche sur le traitement par de hautes doses de médroxy-progestérone de malades atteintes de cancer du sein et ayant subi auparavant de lourds

traitements par d autres méthodes, 7 malades sur 25 ont eu une rémission partielle d une durée mediane de 5 – mois Chez 7 autres malades la maladie est devenue stationnaire En utilisant l'echelle de Karnofsky une amelioration médiane de 20 points a été obtenue chez ces 14 malades. Chez 4 des 15 malades qui n avaient pas repondu au traitement par Tamoxifen, une remission partielle a suivi le traitement par MAP Les malades ont bien toleré le MAP

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ADENOID CYSTIC CARCINOMA (CYLINDROMA) IN THE HEAD AND NECK

A clinical review of 82 cases

B ZIELKE TEMME and M WANNENMACHER

A retrospective analysis was performed at the University Clinics in Münster of the clinical data of patients treated for adenoid cystic carcinoma (cylindroma) in the head and neck Adenoid cystic carcinoma was first described by ROBIN (1853) who called the tumour tumeur hetéroadenique BILLROTH (1856) named it Zylindrom In 1953 FOOTE & FRAZELL introduced the term adenoid cystic carcinoma which now has replaced the older names

Adenoid cystic carcinoma develops in the major and *minor* salivary glands paranasal mucous glands mucous membranes of the *nose* and accessory nasal sinuses upper respiratory passages lacrimal glands (RÖBEL 1971) ceruminal and sweat glands and in the breast (ALBERTINI 1974)

A case of adenoid cystic carcinoma of the Gasserian ganglion region has also been reported (WILLSON & ROSEN 1974) The tumor is *found* most frequently in the *minor* salivary glands of the palate (ENEROTH et coll 1968) Some data from the literature on the incidence in the major and minor salivary glands and in mucous glands appears in Table 1

Though adenoid cystic carcinoma is not a common disease it requires special attention because the prognosis depends largely on adequate initial treatment

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Table 1

Incidence of adenoid cystic carcinoma

Author	Year	No of cases	Incidence (per cent)
Tumours of the major salivary glands			
Koblin & Koberg	1972	215	3 2
Foote & Frazell	1953	877	4
Rafla Demetrious	1970	268	5 2
Tumours of the mucous and minor salivary glands			
Fine et coll	1960	79	16
Koblin & Koberg	1972	125	33 6
Rafla Demetrious	1970	139	28 8
Thackray & Lucas	1960	80	37 5

MANN 1958 SCHETTLER & KOBLIN 1973) This tumour is characterized by slow growth (KNAK & BRANDT 1967 RAMSDEN et coll 1973 STEINHOFF et coll 197 STIEBITZ 1968) frequent recurrence and systemic spread even after long ter survival without disease (SCHETTLER & KOBLIN) General well being may continu for a long time while the tumour progresses (FLETCHER 1973 RÖBEL) These feature as well as the low incidence of this tumour account for the rather conservativ therapeutic management in the past

In recent literature (GABKA & BEYER 1972 SCHETTLER 1972 STIEBITZ 197 WANNENMACHER 1972) it has been emphasized that at present the treatment c choice is radical surgery Pulmonary metastases should not exclude a patient fro surgery since these may grow slowly and without symptoms (FUCHIHATA et col 1973 WANNENMACHER & SCHUTZ 1971) Long term follow up is essential an should not be limited to a certain period (MORAN et coll 1961 SCHETTLER & KOBLIN)

Nowadays the value of modern radiation therapy has been established In 195 NAUMANN still reported no encouraging experiences with irradiation of adenoi cystic carcinomas and KNAK & BRANDT were of the same opinion in 1967 RÖBE considered only limited indications for radiation therapy because of the ques tionable sensitivity to radiation

SCHERER et coll (1972) have pointed out that these negative results were obtaine before the introduction of ^{60}Co and megavolt therapy Thev have stated tha adenoid cystic carcinoma is definitely sensitive to radiation

Modern textbooks give technical directions for the therapeutic management FLETCHER (1973) is of the opinion that all histologic types of tumour are possibl to control equally well by radiation therapy and MOSS et coll (1973) consider adenoid cystic carcinomas even more sensitive to radiation than other malignan

lesions of the salivary glands Maximum tolerated doses for extended target volumes are proposed by these authors and by ARNDT (1973) who favours post operative irradiation Extended target volume is emphasized because of the characteristic tendency to invade nerve sheaths and to spread far beyond the clinically apparent margins of the lesion

Good palliation but no cure was reported by STEINHOFF et coll (1973) in 6 of 30 cases treated by irradiation Better results were obtained by FUCHIHATA et coll from combined surgical and radiologic treatment in a series of 18 cases Four patients primarily irradiated with 9 000 to 10 000 R were reported to be free of disease after 5 years

In their review of 134 cases of adenoid cystic carcinoma CONLEY & DINGMAN (1974) do not give the number of patients irradiated Their indications for radiation therapy are (1) non resectable recurrences (2) to control tumour growth when the margins after surgery are not free of tumour (3) to gain temporary local control in patients in too bad a condition for operation The same indications have been employed in the present series as well CONLEY & DINGMAN found that irradiation proved to be an effective and indispensable adjunct in the management of the majority of these patients Based on 68 irradiated cases in a series of 94 STEWART et coll (1968) conclude radiotherapy has made a very positive contribution to the management of these tumours They outline the problems encountered in evaluating the merits of radiation therapy as follows Surgical accessibility and local radiation tolerance vary enormously from site to site making it difficult to group cases for purposes of comparison The general policy over the years has been that where tumour is accessible surgery should play the primary role radiotherapy being reserved for inoperable or recurrent cases This makes the comparison of like with like impossible The radiotherapeutic approach in respect to target volume technique and dose has varied very considerably over the period in question thus precluding grouping by treatment technique The symptom free control of the primary growth including no progress was used as the criterion of success of treatment They point out that, following high doses tumour residues may remain static and symptom free for many years and that this is especially important for the elderly or for patients known to have metastases

Material and Method of treatment

The material consisted of 82 patients treated between 1958 and 1976 for adenoid cystic carcinoma in the head and neck Complete clinical follow up data were available for 76 of the patients Forty three patients were irradiated and 36 were treated by operation only in 3 cases no specific treatment was given

In spite of all shortcomings retrospective analysis seems justified in view of the fact that adenoid cystic carcinoma is a rare tumour and a long term follow up is necessary to assess the treatment results

Table 2

Tumour location

Tumour site	No of patients
Major salivary glands	25
Parotid	16
Submandibular	7
Sublingual	2
Minor salivary and intraoral mucous glands	42
Palate and maxillary antrum	27
Tongue	7
Lip	2
Buccal mucosa	2
Epipharynx	2
Floor of mouth	1
Lower jaw	1
Other sites	15
Trachea and bronchi	6
Larynx	2
Nose	2
Orbit	2
Auditory canal	2
Neck	1

Tumour site Of the tumours 31 per cent were located in the major salivary glands, 51 per cent in intraoral mucous or minor salivary glands and 18 per cent of the patients had adenoid cystic carcinoma in other regions of the head and neck (Table 2) The most common sites were the hard and soft palate

Age and sex distribution At the time of diagnosis the age of t from 15 to 81 years (mean 55 4 years) 68 per cent of the patie and sixth decade (Fig 1)

Six patients with adenoid cystic carcinoma of the trachea treated at an average age of 48 5 years which means that ($p<0$ 1) younger than th other patients

The mean ages of patie with tumours of the major were 57 and 56 3 years resp

KOBLIN & KOBERG (1972) repo that on an average occur 7 3 years later in intraoral ry glands than in This statement was not confirmed in he present series

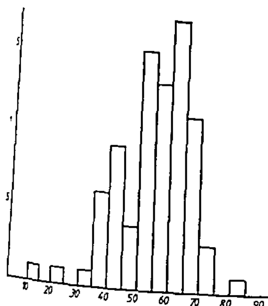


Fig 1 Age distribution at time of diagnosis

Of the patients 52 (63 per cent) were females 30 (37 per cent) were males 7 of the 9 patients under 40 years of age at the time of presentation were women In the literature were found 656 cases Of these 54 per cent were females and 46 per cent males female preponderance thus being statistically significant (p<0 05)

Tumour si e In most cases the clinically assessed diameter of the tumour at the time of presentation was given in 13 cases the data were incomplete Detailed retrospective tumour classification according to stages as proposed for carcinomas by the UICC was not undertaken since it did not appear to be useful in view of the various tumour sites the number of patients and the different modes of treatment The diameter of the tumour was smaller than 2 cm in 11 patients more than 5 cm in 30 cases In 28 cases the diameter varied between those two figures The average tumour size for 22 patients who were free of disease for 5 or more years after the initial treatment was 3 0 cm in diameter In 16 patients with recurrence within 5 years after the initial treatment the mean tumour size was 5 8 cm

Duration prior to treatment The interval between first symptoms and initial treatment ranged from a few days to 10 years mean duration was 1 7 years (Fig 2) The impression is that patients with adenoid cystic carcinoma do not have a long history The present data are close to those reported by ENEROTH (1968) 37 cases with a mean duration of 1 9 years GABKA & BEYER MORAN et coll and SCHETTLER report a mean duration of 2 6 3 5 and 4 5 years for 32 53 and 53 patients respectively

Methods of treatment The methods of treatment and the number of patients are given in Table 3 Radical surgery if possible has frequently been advocated in

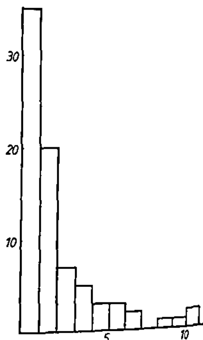


Fig 2 Interval between first symptom and primary treatment

recent literature (FUCHIHATA SCHETTLER & KOBLIN STIEBITZ 1972 WANNENMACHER) Accordingly a change in the mode of treatment has occurred in the present series From 1957 to 1968 radical surgery was performed in 14 patients 22 patients received less extensive operations From 1969 to 1976 20 radical and 17 non radical operations were performed

Radiation therapy was applied at all stages of the tumour disease In 6 inoperable patients irradiation was the initial treatment The tumour doses applied ranged from 55 to 85 Gy

Postoperative irradiation was given to 5 patients after radical surgery and to 18 patients after non radical operation The average dose applied was 51 Gy Three patients received total doses of more than 60 Gy and 3 less than 50 Gy (2 of these before 1961)

Local recurrence was irradiated in 25 patients 15 of these received postoperative irradiation after repeated surgery In 10 cases radiation therapy alone was administered Metastases of the lungs were irradiated in one patient

In most cases (34 patients) ^{60}Co irradiation was given 3 received electron beam and 6 megavolt irradiation In one case of recurrent disease 30 Gy were given intraoperatively with a ^{90}Sr source since tolerable skin doses had been reached by prior treatment

Results

Two years after the initial treatment 79 per cent (56/71) were living free of disease and 13 per cent (9/71) were living with disease Six per cent (4 patients) had died of their tumours and 2 patients had died of intercurrent disease

Table 3

Methods of treatment

	No of patients	Irradiation	No irradiation
No surgery	9	6	3
Non radical surgery	39	27	12
Radical surgery	34	10	24
Total	82	43	39

Table 4

Remission

Method of treatment for recurrent disease	No of cases	Years			
		1	>2	>3	5
Operation and irradiation	16	11	6	5	3
Operation only	10	8	4	1	—
Irradiation only	10	5	2	1	1
No therapy	5	2	—	—	—

Five years after treatment 52 per cent (26/50) were living free of disease 22 per cent (11/50) were living with disease and 26 per cent (13/50) had died of their tumours Ten years after treatment 17 per cent (3/28) were living free of disease 39 per cent (11/28) were living with disease and 46 per cent (13/28) had died of their tumours One patient had died of intercurrent disease None of the 3 patients living 15 years after treatment was free of disease 6 had died of their tumours and one of intercurrent disease

Determinate survival rates were calculated for the patients 2 5 10 and 15 years after treatment 4 patients who had died of intercurrent disease were excluded from the calculations In Fig 3 the survival rates are given separately for 3 different groups of sites and for patients treated by radical or non radical surgery In each case the percentage of patients living free of disease after the initial treatment is shown separately

Seven patients who were inoperable because of extensive tumour or for other reasons were observed for 2 or more years Of these 5 patients had persistent or recurrent disease one was free of disease 4 years after irradiation Four of the patients were followed for 5 years after treatment all died of their tumours within that period

Table 4 gives the number of patients free of symptoms 1 2 3 and 5 years after different treatments for recurrence Though the number of cases is small in each group it is apparent that combined surgical and radiologic efforts give the best re

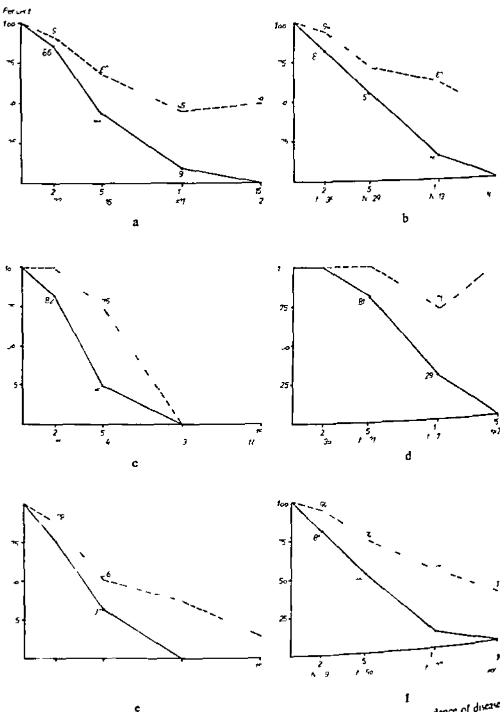


Fig 3 Determinate survival rates (upper curves) and rates of patients with no evidence of disease after first specific treatment N is the total number of patients in each group at a specific time The group consisted of patients with a) tumours in the major salivary glands b) tumours in the minor salivary glands c) tumours in other sites d) tumours treated by radical surgery e) tumours treated by non radical surgery f) and all cases of adenoid cystic carcinomas

Table 5

Local recurrence

Local recurrence within year	No of patients
1	8
2	1
3	3
4	4
5	2
6	4
7	3
8	2
9	1
10	2
Total	30

...lts 5 years after surgery and subsequent irradiation 3 of 16 patients were still free of symptoms

Adenoid cystic carcinoma of the trachea is associated with special treatment difficulties The present series included 6 cases The patients were middle aged and the diagnosis had been delayed by unspecific treatment for periods from 1 to 6 years Radical surgery was usually impossible because of the tumour location Also the radiation therapy encountered difficulties Two patients died after 2 and 5 months respectively from treatment complications 2 other patients died 4 and 5 5 years after presentation and 2 patients are living with disease Thus the prognosis is worse than in other tumour locations

Local recurrence When the period in which the patient is free of symptoms is very short it becomes impossible to distinguish between recurrent and persistent diseas By evaluating all clinical records available an effort was made to be as accurat as possible Six patients were considered to have persistent disease 4 of these being inoperable

In 30 patients local recurrence occurred Eight patients were free of symptoms for less than one year 3 of these had not been operated upon In 10 patients the disease free intervals ranged from 1 to 5 years after the initial treatment No recurrence occurred after more than 10 years (Table 5) Fourteen of the 30 patients had distant metastases as well

Eight radically operated patients stayed free of disease for 5 3 years on an avera e 21 treated by less extensive surgery developed recurrence after a mean period of 3 7 years 7 inoperable were free of symptoms for 4 months on an average These figures cannot be compared directly because the situation at the time of

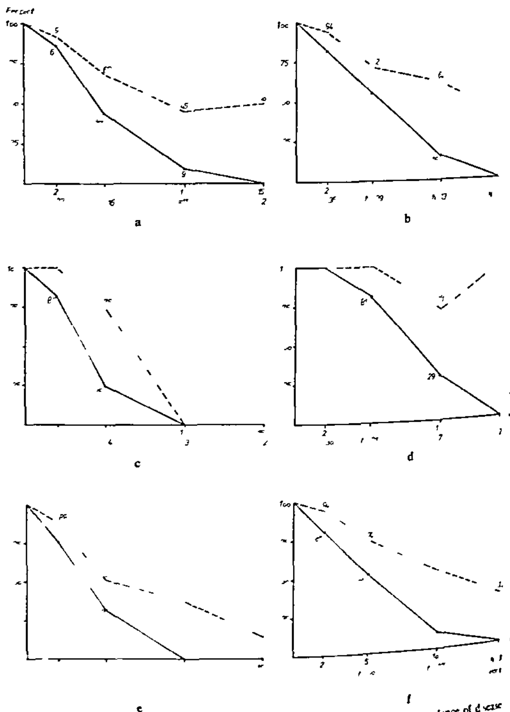


Fig. 3 Determinate survival rates (upper curves) and rates of patients with no evidence of disease after first specific treatment N is the total number of patients in each group at a specific time The group consisted of patients with a) tumours in the major salivary glands, b) tumours in the minor salivary glands c) tumours in other sites d) tumours treated by radical surgery e) tumours treated by non radical surgery f) and all cases of adenoid cystic carcinomas

oid tumours depends largely on the size and location of the lesion and on adequate primary treatment For an analysis of the treatment results at least 10 years of observation are necessary because of the natural history of the tumour Poor long term survival rates have been reported previously which may be attributed to the fact that radical surgery was not generally accepted Anyhow this holds true in the present series in which the primary treatment was given about 15 years ago Nor was extended field hi h dose radiation common at that time The present series indicates that these methods of primary treatment must be employed to improve the prognosis of this tumour When an extended tumour unfavourable location or recurrent disease limit the possibilities of curative treatment at the time of presenta ... palliative surgery and adequate irradiation should be employed since long term remissions are possible to achieve These methods of treatment are especially valuable for the elderly patient No treatment at all is evidently the worst policy In spite of remarks in the literature emphasizing absence of sensitivity to radiation long term palliation is possible A long term clinical follow up should be carried out carefully in order to make possible early treatment in case the disease should recur A patient with metastases should not be excluded from treatment since the metastases may grow slowly and without symptoms

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SUMMARY

A review of 82 cases of adenoid cystic carcinoma in the head and neck is given Radical surgery was carried out in 33 patients and yielded the best long term results Radiation thera y was given to 43 patients for inoperable tumour local recurrence or postoperatively for sub-clinical disease It proved especially valuable in obtaining remissions from local recurrence

ZUSAMMENFASSUNG

Die Arbeit gibt einen Überblick uber 82 behandelte Zylindrome im Kopf Hals Bereich Eine Radikaloperation wurde bei 33 Patienten durchgefuhrt wobei die besten Ergebnisse erzielt werden konnten Bei 43 Patienten wurde postoperativ bestrahlt bzw eine primare Strahlentherapie durchgefuhrt Aus dieser Gruppe ergeben die Kombination von Operation und Bestrahlung die relativ besten Resultate wobei besonders die rezidivfreien Intervalle verlangert werden

presentation differed markedly they are just meant to illustrate the natural histo-
of adenoid cystic carcinoma in general

While 20 of the 36 patients are still living 16 with persistent and recurrent disea
died within 2 5 years on an average after developing local recurrence

Despite the discouraging general course of the disease longlasting individu-
histories occurred One patient with adenoid cystic carcinoma of the tongue die
9 years after a local recurrence 2 patients are alive 11 years after treatment fo
their first recurrence One of these patients is now free of symptoms 3 years after h
fifth operation for recurrent tumour of the parotis gland the other is living wi
extensive recurrence after 7 operations and 5 series of irradiation for a tumou
originating in the palate

Metastases In 24 patients generalisation of the tumour occurred of these 1
also developed local recurrence

For 12 of 82 patients no chest films were available Of the remaining 70 patient
15 (21 %) had pulmonary metastases 2 already at the time of presentation In 1
patients metastases were detected on an average of 3 years after initial treatmen
One year later 11 of these 13 patients were still living after 2 years 7 patien
were alive and after 3 years 10 of 13 had died One patient underwent surgery
years after pulmonary metastases had been detected and died 10 years later of
heart attack Such extremely long survivals of generalized disease are frequentl
described in the literature Pulmonary metastases of adenoid cystic carcinoma ar
not as prognostically hopeless as in other carcinomas but on the other hand long
term survivals of more than 3 years are not common

Metastases to other organs were found in 13 patients (16 %) after 4 5 years o
an average In one patient with adenoid cystic carcinoma of the buccal muco-
osteolytic destruction in the frontal region of the skull was recognized 13 year
after initial treatment In 6 patients haematogenic spread to the lungs as well as t
other organs occurred

Discussion

It is evident that curative treatment was the aim of the irradiation in some cases
in others palliation only was attempted In each case the group of patients wa
small Tumour site and extension varied as widely as the histologic grade o
malignancy or the number of prior treatments A comparison of survival rates i
not appropriate under these conditions In order to evaluate the benefits of irradia
tion beyond giving favourable case reports the term remission has been applied to
cases with recurrent disease

Adenoid cystic carcinoma is at present considered to be a malignant tumour It
grows relatively slowly and causes local recurrence and generalized disease even
after long symptom free periods In the present series the duration before treatment
was not as long as is frequently reported in the literature The prognosis as with

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RADIATION EFFECTS ON THE FINE BLOOD VESSELS IN ABDOMINAL ORGANS OF MICE

J EGAWA and K ISHIOKA

In radiation therapy of malignant diseases the relative radiation effects on t tumour and on the normal tissues play an important role for the curability (PATE SON 1963) The tolerance limit of the normal tissues may be due to the sensitivity the vascular system Irradiation of tissues causes early morphologic and function changes in the blood vessels Also late radiation effects on the vascular system ha been reported (KAWAMURA & FUJIWARA 1973 RUBIN et coll 1964 ELLINGER 195 JOLLES & HARRISON 1966 DEVIK 1955 HOLLAENDER 1956 MOSS & GOLD 196 HASSLER & MOVIN 1966)

Various techniques for demonstration of the fine vascular structure as angiograph the India ink gelatin mixture (KAWAMURA & FUJIWARA ANGULO et coll 195 JEE & ARNOLD 1960 TIBOLDI et coll 1968) and methods utilizing filling of the vessel with various contrast material (BISHTON & ROGERS 1950 HASSLER 1964) have bee extensively used for recording of capillary injury and changes in the vascular struc ture after irradiation (KAWAMURA & FUJIWARA RUBIN et coll ELLINGER JOLLES & HARRISON DEVIK HOLLAENDER HASSLER & MOVIN RUBIN & CASARETT 1966) In order to analyze the effect of radiation on the abdominal organs (small intestine stomach liver kidney and spleen) the resin cast method (BATSON 1955 MURAKAM 1971) was applied and the results are now reported

Submitted for publication 13 November 1977

Table 1

Number of animals examined after different periods Animals that died before the planned observation time are given in parentheses

Dose	Days after irradiation	No of mice	
		ddN	WH HWT
5 Gy	1	3	3
	2	3	3
	3	3	3
	10	6	
	30	6 (2)	
10 Gy	1	6	3
	2	6	3
	3	6	3
30 Gy	1	6	
	2	6	
	3	6 (–)	
Non irradiated controls	—	15	6

Material and Methods

…imals and irradiation technique Seventy two (including 15 controls) ddN albino …n mice (females average weight 25 g) and 24 (including 6 controls) WH/HWT …o strain mice (males weight about 20 g) were used (Table 1)
The animals were divided into four groups non irradiated controls and animals …radiated with 5 10 and 30 Gy respectively The irradiated animals received one …l treatment with a gamma ray beam from a telecobalt unit (SSD 80 cm field …e 30 cm × 30 cm dose rate 0 45 Gy min) The radiation beam was calibrated with …lorex dosimeter The animals were killed after different periods Two animals …ed during the experimental period

Preparation of the resin The base of the resin was methyl methacrylate monomer …fore injection the resin had to be freshly prepared First 2 4-dichloro-benzoyl …oxide (catalyst) was added to the monomer up to a final concentration of 2 per cent …e mixture was then warmed to about 75 C and thereafter rapidly cooled Then …zoyl peroxide (catalyst) was added and just before the injection into the animal …ethylanilin (accelerator) up to 2 per cent
This preparation technique of resin was a modification of the method of MURA …

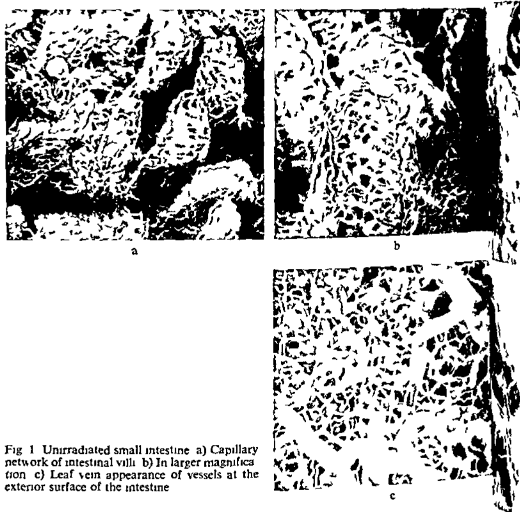


Fig 1 Unirradiated small intestine a) Capillary network of intestinal villi b) In larger magnification c) Leaf vein appearance of vessels at the exterior surface of the intestine

Resin injection and corrosion casting The animals were anesthetized with ethylether and decapitated and then irrigated with Ringer solution through the aorta The prepared mixture (subpolymerized state) was injected into the thoracic aorta under moderate pressure The injected animals were placed in hot water (60–70 C) and kept at about 70 C in an incubator After a few hours sodium hydroxide (about 20) was added for corrosion of the soft tissues The resin casts obtained were washed and dried with ethyl alcohol in air

Scanning electron microscopy The dried whole body resin cast was dissected and sliced The sliced resin casts were fixed on an aluminium block with a silver paste and then exposed to vacuum evaporation with carbon and gold These casts which were coated by electron dense materials were examined and photographed with a scanning electron microscope (model MSM-4 Hitachi Japan) By this method not only the arterial system but also the capillary and venous systems were demon



Fig. 2 The capillary network of the intestinal villi at 30 days after irradiation with 5 Gy Capillaries at the top of villi partially destroyed

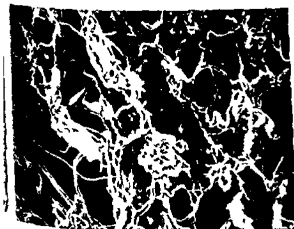


Fig 3 Capillary network of the intestinal villi at 3 days after irradiation with 10 Gy markedly reduced

strated It is difficult to discriminate these two systems at their terminal regions but as a rule the venous system is possible to recognize since the veins are thicker in the postcapillary region

Results

No significant differences were observed between the two strains of mice

The resin cast method could distinctly demonstrate the shape of the small blood vessels contrary to other methods The characteristic appearance of the vascular network is illustrated in the figures

Small intestine The vascularity of the small intestine can be classified into 4 groups the mucosal submucosal muscular and subserosal vessels By the scanning electron microscope three of these groups could be observed namely the mucosal the muscular and the subserosal vessels The mucosal vessels *formed* a characteristic

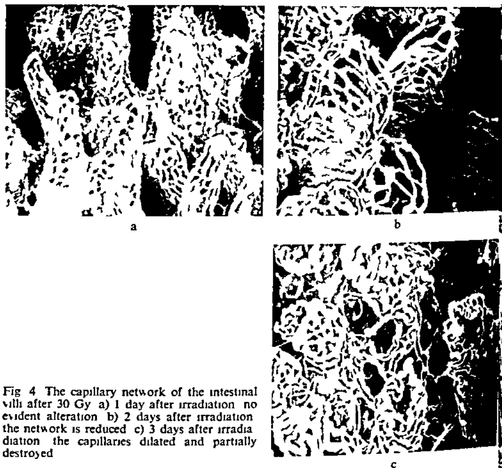


Fig 4 The capillary network of the intestinal villi after 30 Gy a) 1 day after irradiation no evident alteration b) 2 days after irradiation the network is reduced c) 3 days after irradiation the capillaries dilated and partially destroyed

network Its general appearance was the same as that of the intestinal villi with a regular reticular arrangement (Fig 1) The muscular and subserosal vessels branched off from the large blood vessels at the exterior surface of the intestine in a way similar to leaf veins

In contrast to the non irradiated mice both the general arrangement of the vessels and the shape of the capillaries themselves were changed in the irradiated animals At 10 days and 30 days after a single whole body irradiation with 5 Gy the capillary network at the top of the intestinal villi had been partially destroyed (Fig 2) At 3 days after 10 Gy (Fig 3) and 2 days after 30 Gy (Fig 4 b) similar alterations were observed and the capillaries were reduced in number These changes were more extensive than after 5 Gy but the diameter of the capillaries was rather uniform after the different exposures At 3 days after 30 Gy marked vascular dilatation had occurred and the capillary diameters were not uniform (Fig 4 c) The vascular network at the top of the intestinal villi had been partially destroyed The vessels at the exterior of the intestine were not changed No obvious alterations could be found at 1 2 and 3 days after 5 Gy and at 1 and 2 days after 10 Gy and at 1 day after 30 Gy

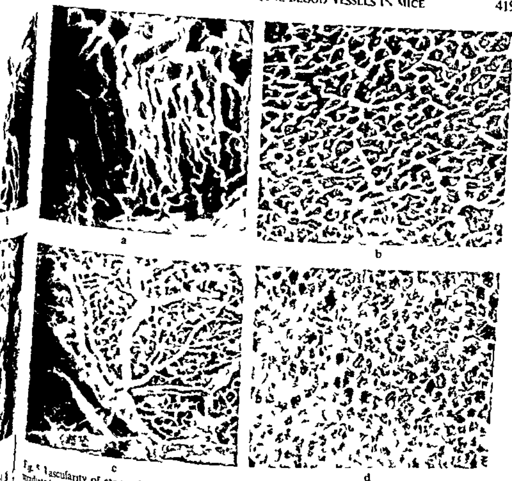


Fig. 5 Vascularity of stomach a) Capillaries arranged perpendicularly to the stomach wall Non irradiated control b) Honeycomb appearance of vessels at inside of stomach c) Leaf vein appearance of vessels at outside of stomach Non irradiated control d) Honeycomb appearance of vessels at 3 days after irradiation with 10 Gy The vessels are narrower than normal

Stomach The vascular system of the stomach can be divided into 5 groups the mucosal vessels the vessels around the muscularis mucosae the submucosal muscular and subserosal vessels The mucosal muscular and subserosal vessels were possible to observe The mucosal vessels were arranged perpendicularly to the stomach wall and the top of these vessels form a characteristic network with a honeycomb-like shape The muscular and the subserosal vessels had an appearance similar to the branched vessels of the small intestine At 3 days and 2 days after 30 Gy and 3 days after 10 Gy the perpendicularly arranged vessels seemed to be coarser and the honeycomb-like vessels thinner than normally but these changes were not quite certain (Fig 5)

Liver The vessels at the liver surface were in the non irradiated mouse arranged radially from the central veins and had a characteristic shape Also the vascular

Table 2

Irradiation effects on the capillaries of different organs Uncertain effects are given in parenthes

	Days after irradiation at										
	5 Gy					10 Gy			30 Gy		
	1	2	3	10	30	1	2	3	1	2	3
Intestine	–	–	–	+	+	–	–	+ +	–	+	
Stomach	–	–	–	–	–	–	–	(+)	–	(+)	( )
Liver	–	–	–	–	–	–	–	–	–	–	
Kidney	–	–	–	–	–	–	–	–	–	–	
Spleen	–	–	–	(+)	(+)	–	–	–	–	–	–

network in cross sections of the liver cast had a similar radial arrangement Th vascular distribution in the liver was more dense than in the other organs No radia tion effects could be distinctly observed in any of the irradiated groups

Kidney At the surface of the kidney the vessels were arranged as a reticular net work At the interior part of the kidney the vessels ran radially from the renal pelvi through the medulla to the cortex In perpendicular sections these bundles of bloo vessels had a honeycomb like structure Through the spaces of the honeycomb other bundles of blood vessels passed In the cortex branching vessels were demon strated and also capillary structures constituting the renal glomeruli The vasculari of the kidney was very dense No obvious radiation effect on the renal vessels wa found in any of the experimental groups when compared with non irradiated controls

Spleen The vascular system of the spleen consisted of branching vessels and ir regular lumps with sinusoid like vessels The vascularity at 10 days and 30 days afte 5 Gy seemed to be somewhat reduced These observations were however not quit evident and it was not possible to exclude artefacts introduced by the high pressur at which the resin must be infused into the spleen

The capillary changes due to irradiation are summarised in Table 2

Discussion

The technique applied the resin cast method demonstrated the fine vascula morphology better than other previously used methods (ANGULO et coll JEE & ARNOLD 1960 TIBOLDI et coll BISHTON & ROGERS HASSLER RUBIN & CASARETT 1966) Irradiation of the different tissues and organs resulted in changes of their structure which modified the appearance of the vascularity The changes of the vessels might be considered as secondary to injury of the surrounding structures A direct radiation effect on the capillaries may also occur but is not possible to prove

with the methods used An indication that such an effect may exist is known A capillary cast of the intestine made as soon as 3 days after irradiation with 30 Gy demonstrated irregular thickness and widening of the capillary diameters compared to the control group

Previously early physiologic radiation effects on the vessels have been observed as permeability changes demonstrated by use of dye or colloid but not as morphologic changes Several authors have reported that the early changes of the capillaries are of a purely functional type but that apparent morphologic changes can be observed only at a later stage and after large doses of radiation (ELLINGER HOLLAENDER HASSLER & MOVIN RUBIN & CASARETT 1968)

Necrosis of important tissues after irradiation causes problems in the clinical situation Injury to the capillaries has been registered as one of the main causes of necrosis The present results show that early changes of the vascularity of several tissues may occur but further investigations of the late radiation effects on the vascularity are motivated

Acknowledgements

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SUMMARY

The capillary networks of normal and irradiated abdominal organs of mouse were investigated by a resin cast technique The structure of the capillary system had characteristic appearances. Radiation effects on the fine vascular structures were demonstrated from one to 30 days after a single dose of 5 to 30 Gy whole body irradiation Prominent morphologic abnormalities of the shape and distribution of the capillaries were identified especially in the small intestine

ZUSAMMENFASSUNG

Das Kapillarsystem der Abdominalorgane von normalen und bestrahlten Mausen wurde mit Hilfe einer Harzgusstechnik untersucht Die Struktur des Kapillarsystems hatte ein charakteristisches Aussehen. Die Strahlungseffekte auf die feinen Gefasse wurden zwischen einem und 30 Tagen nach einer einmaligen Dosis von 5 bis 30 Gy Ganzkorperbestrahlung beobachtet. Deutliche morphologische Veranderungen des Aussehens und der Verteilung der Kapillaren besonders im Dunndarm, wurden festgestellt

RESUME

Le reseau capillaire d organes abdominaux de souris normales et de souris irradiees a ete étudié par une technique de moulages par une resine La structure du systeme capillaire a des aspects caractéristiques L effet des radiations sur les fines structures vasculaires a été mis en évidence de 1 a 30 jours apres une dose unique de 5 a 30 Gy d irradiation corporelle totale Des anomalies morphologiques importantes de la forme et de la distribution des capillaires ont ete identifiees en particulier sur l intestin grêle

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SKIN REACTIONS IN MOUSE BY FRACTIONATED NEUTRON IRRADIATIONS WITH THE SAME NSD_n

SHOZO SUZUKI

Since the failure of fast neutron therapy about forty years ago (STONE et coll. 1940, STONE & LARKIN 1942), it was considered disadvantageous by virtue of the excessive late effect on normal tissues (STONE 1948), until it was revealed that excess doses were given to STONE's patients (SHELINE et coll. 1971, BEWLEY et coll. 1963) and that fast neutrons having high linear energy transfer (LET) could be effective for killing hypoxic cells in tumours because of their low oxygen enhancement ratio (OER) (GRAY et coll. 1953, THOMLINSON 1963, ALPER 1963, FOWLER et coll. 1963). On this basis, radiation therapy with cyclotron produced neutrons was begun again at the Hammersmith Hospital in England and also in the United States and Japan during the past decade.

The neutron therapy was planned also in this institute in 1970, and its irradiation regimen was two fractions a week, due to a limited availability of machine time. It was therefore required that the effect of neutron irradiation on normal tissues, especially the skin, had to be determined for this new dose fractionation, because little was known of its effect and because normal tissue tolerance determines the irradiation dose.

The experiments were performed to analyze three different dose fractionations (two fractions a week) from which NSD_n of normal tissues was calculated by means of the Hammersmith Hospital method. According to Ellis' formula for neutrons (FIELD 1972) the effect of these fractionations would not differ, but experiments seemed necessary for a confirmation of the validity of these new fractionations

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Table

Dose fractionations given two times a week with the same NSD

Group	Total dose (Gy)	Dose per fraction (Gy)	No of fractions	Time (days)
I	15 00	1 25	12	39
II	14 60	1 46	10	32
III	14 08	1 76	8	25

before they were used as therapy regimens The therapy was started in Novem 1976 (IINO & KUMASAWA 1977) Apart from the therapeutic use the effects of si dose of fast neutrons roentgen rays and ^{60}Co γ rays were also examined

Materials and Methods

To obtain the new fractionations given two times a week and equivalent to Hammersmith Hospital method i e 14 4 Gy (1 440 rad according to the Hammersmith rad which was devalued by a factor of 1 08 SMITH et coll 1! given in 12 treatments over 26 days (CATTERALL 1974) the following ELLIS form for neutrons was used

$$\text{Total dose} = NSD_n \times N^{0\ 04} \times T^{0\ 11}$$

where NSD_n is the nominal standard dose for fast neutrons N is the number of f tions and T is the over all time in days The new fractionations calculated are g in the Table

The assessment of radiation induced injury to the skin was carried out with skin transplantation method of KAL et coll (1974) with slight modifications hair of skin of donor and recipient mice was removed with a hair-clipper an depilatory a few days before transplantation The skin field about 17 mm diameter on the back of white DDD mice was irradiated with fast neutrons thro two collimators for therapy and for this experiment and according to the fractic tion regimen given in the Table Circular pieces of the skin 10 mm in diameter w excised and placed on the back of the recipient mice in which graft beds had b prepared by excision of similar but slightly smaller pieces of skin The transplantat was performed by rubbing edges of the skin with very small amounts of α-cya acrylate The grafted skin pieces were covered with sterilized gauze and then fi with vinyl tape and pressure elastic grip bandage for one to two weeks Brc (DDD C3H/He)F_1 hybrid mice were used as recipients to avoid immunolc complication and to distinguish the grafted skin clearly The ratio of the treated a untreated areas of grafted skin remaining for three months was used as a parame

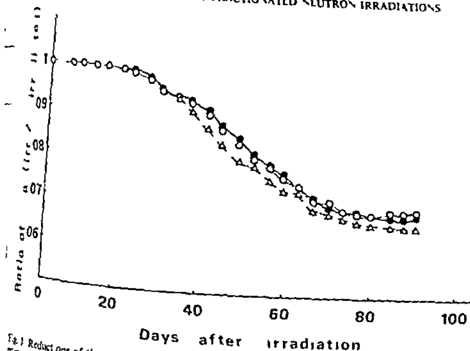


Fig 1 Reductions of the area of skin grafts by fractionated neutron irradiation relative to that of unirradiated ones A dose per fraction of each group is 1.25 Gy (O) 1 46 Gy (●) and 1 76 Gy ( ) (1 the table for details of the fractionations For clarity representation of standard deviations is omitted in the figure but the differences among the 3 groups are insignificant

for skin injury Part of the skin irradiated mice had been bred for a certain period for observation of possible change in the irradiated skin

Fast neutrons ($\bar{E}_n = 6$ MeV) with a dose rate of 200 mGy/min were produced by bombarding the thick beryllium target with 50 μA of 15 MeV deuterons accelerated with the cyclotron of the institute Roentgen rays were generated by a therapy unit operated at 200 kV and 25 mA and were filtered through 0 3 mm Cu and 1 mm Al The dose rate was 900 mGy/min ^{60}Co γ rays were obtained from a therapy unit at a dose rate of 564 mGy/min Irradiation of the skin by these types of radiation was performed without the use of build up materials

Results

The ratio of the irradiated skin graft area to that of unirradiated controls appears in Fig 1 A decrease began about three weeks after the irradiation and approached constant value after about 70 to 80 days No significant differences were observed between the three fractionations (1 25 1 46 and 1 76 Gy per fraction) The result suggests that a fractionation two times a week even with a high dose per fraction is therapeutically applicable at least from the standpoint of the skin reaction of mice since the observed slight injury may be considered permissive However it remains

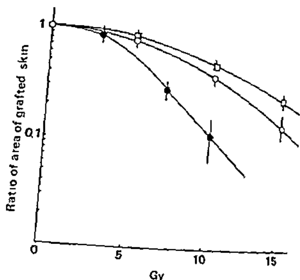


FIG 2 Reductions of the area of skin grafts irradiated with single doses of fast neutrons (●) roentgen rays (○) or ^{60}Co γ rays (□) relative to that of unirradiated ones

uncertain whether the mouse skin (especially the basal cells of epidermis) respo[nds] as does the human skin to fast neutrons although similar RBE has been report[ed] (FIELD & HORNSEY 1971) The result also demonstrates the applicability of Ell[is] formula for fast neutrons

High single doses of fast neutrons roentgen rays and ^{60}Co γ rays produce[d] marked differences in skin injury (Fig 2) The injury was slight at a dose of 3 Gy [of] fast neutrons but increased gradually at higher doses Roentgen rays and ^{60}C[o] γ rays also gave qualitatively similar but quantitatively lesser effects on th[e] sk[in] ^{60}Co γ rays were least effective The doses at which 50 per cent of the skin wa[s] injured were 5 5 8 5 and 10 5 Gy of fast neutrons roentgen rays and ^{60}Co γ rays respectively These lead to the RBE values of fast neutrons and ^{60}Co γ rays for 5[0] per cent of skin injury being 1 6 and 0 8 respectively The values mean that the ski[n] impairment with fast neutrons is less than that with roentgen rays as has been expected from their build up because the RBE of fast neutrons for most normal and malignant cells are 2 to 3 at 50 per cent level of surviving fractions

DISCUSSION

As predicted from Ellis formula the result showed that for a given total dose the injury to the skin irradiated two times a week was small Moreover the effect of a high dose per fraction was not different from that of a low dose per fraction This is in good accordance with the death of mice from radiation pneumonitis (HORNSEY et coll 1975) and implies the possibility of a therapy with a high dose per fraction for a short period Likewise a high dose per fraction is known to be superior because small numbers of hypoxic cells in tumours are not sterilized effectively at lower doses (FOWLER & MORGAN 1963) However if a high dose per fraction is adopted in the therapy it is strongly required that the dose per fraction be increased step by step with attention to skin impairment

Two points must be discussed further First the present work was performed ... to the old Hammersmith rad Thus 15 6 Gy (1 560 rad) of total dose ... of 14 4 Gy should have been used to calculate NSD_n For the present purpose ... seemed inadequate that consequently NSD_n of normal tissues was underestimated ... the experiment. However as the skin injury occurred even under the condition ... NSD, (Fig 1) the result would be significant not only in terms of the inter comparison of the three different types of radiation which had the same NSD_n (Orton & Ellis 1973) i e 92 per cent of NSD_n but also in comparison with other ... ments e g three fractions a week Secondly the neutron dose used includes ... dose as does United States neutron dose while the Hammersmith neutron dose does not. However the difference can almost be ignored in terms of biologic effective ... for the following reasons (1) contamination of neutrons with γ rays is only ... per cent at the tissue surface and (2) RBE of γ rays is about three times lower than that of neutrons at low doses

Most work on injury to the skin has been carried out using the method of ... the skin reaction by direct observation but little work has been done using the transplantation (Kal et coll) For this reason the method of skin transplantation ... adopted in the present work although the relation between the two methods ... well understood However it may be likely that either the extent of injury ... the RBE produced by the methods differ because for example the RBE for skin ... appeared lower as evaluated by the method of transplantation than by scoring.

A high single dose affected the skin more than did the fractionated doses This could possibly be due to occurrence of repair and repopulation in the intervals of and ... fractionated irradiation (Denekamp & Field 1974)

Acknowledgements

The author is greatly indebted to Dr G Fujii Department of Surgery for valuable comments on skin transplantations and to Mr S Sakai for operation of the cyclotron

SUMMARY

The results of three fractionations of neutron irradiation with the same NSD_n were examined for skin reactions in mice No significant differences were observed between these fractionations given two times a week (15 Gy/12 fractionations/39 days 14 6 Gy/10 fractions/32 days and 14 08 Gy/8 fractionations/25 days) The result suggests the value of high dose per fraction given two times a week

ZUSAMMENFASSUNG

Die Resultate der Fraktionierung von drei Neutronenbestrahlungen mit der gleichen NSD_n wurden hinsichtlich der Hautreaktionen von Mäusen untersucht Keine signifikanten Unterschiede zwischen diesen Fraktionierungen die zweimal wöchentlich gegeben wurden (15 Gy/12 Fraktionen/39 Tage 14 6 Gy/10 Fraktionen/32 Tage 14 08 Gy/8 Fraktionen/25 Tage) wurden beobachtet Die Ergebnisse deuten auf den Wert einer hohen Dosis pro Fraktion zweimal wöchentlich verabfolgt hin

RÉSUMÉ

Trois fractionnements de dose de neutrons avec la même NSD_n ont été examinés en qui concerne les reactions cutanées de la souris L auteur n a pas trouvé de différence sign cative entre ces fractionnements donnés deux fois par semaine (15 Gy/12 fractions/39 jou 14 6 Gy/10 fractions/32 jours et 14 08 Gy/8 fractions/25 jours) Ce resultat fait penser qu serait interessant de donner une forte dose par fraction administrée deux fois par semain

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IMATION OF INTERNAL RADIATION DOSE FOR VARIOUS PHYSIQUES USING MIRD ADULT ABSORBED FRACTIONS

HIROSHI YAMAGUCHI

orbed fractions of the Medical Internal Radiation Dose Committee (MIRD) een the most useful for estimating an internal absorbed dose recieved from an ation of a radiopharmaceutical agent (SNYDER et coll 1969) Recent on of the absorbed dose for a number of radionuclides have made a al dose calculation considerably convenient (SNYDER et coll 1974 1975) bsorbed fraction (AF) $\phi(T \leftarrow S)$ is defined as a ratio of energy absorbed in a organ T to energy released in a source organ S The specific absorbed on SAF $\Phi(T \leftarrow S)$ is defined as $\phi(T \leftarrow S)$/(mass of T) (LOEVINGER et coll 1965) nt publications of AF are mainly valid for the adult European and American d man (adult phantom) SNYDER and his collaborators O k Ridge National ratry (ORNL) have attemped preliminary estimations of t age-dependences F and SAF by designing smaller mathematical phantoms (SNYDER & COOK 1971 ER & FORD 1973 HILYER et coll 1972 1973 HWANG et ll 1976 and JONES oll. 1976)

e application of the MIRD adult AF to Japanese physique has been in gated Previously a simple transformation method was found and examined applica spond ng to an individual from the MIRD adult AF and examined the method of it by experiment (YAMAGUCHI et coll 1975) The old transformation method of the target mmarized as follows (1) It consists of two parts transformation of the target

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organ mass and of the distance between S and T The former is represented ratio of the target organ mass for the actual individual and for the standard m The latter was given by approximating the variation of SAF with distance in human body with the traditional exponential form and by introducing two pa meters the effective distance and the scale factor The effective distance cha terizes a distance between S and T it was approximated with the distance betw the centres of mass of S and T The scale factor characterizes a change in physi from MIRD phantom to an individual it was approximated with a ratio of th trunk lengths Moreover the energy dependence of the effective absorption coe cient was considered to reduce the error due to the approximation of the ex nential distribution for photon energies from 0 1 to 0 5 MeV The method does consider the cases for photon energies below 0 1 MeV (2) It does not discrimin the case where T is equal to S from the case where T is not equal to S (3) It d not take into account the case where target organ is the skeleton

The present report deals with a new method for estimation of SAF for you persons

Transformation method

AF ϕ' (T ← S') and SAF Φ'(T ← S') of an individual are obtained from the co responding MIRD adult AF ϕ(T←S) and SAF Φ(T←S) by the following equation

$$\phi' (T' \leftarrow S') = S_m \, S(Xg) \, \phi(T \leftarrow S)$$

$$\Phi' (T' \leftarrow S') = S(Xg) \, \Phi(T \leftarrow S)$$

$$S_m = m_T/m_{T'}$$

$$S(Xg) = \overline{\Phi'(X')}/\overline{\Phi(X)}$$

$$\cong f(\varepsilon \, Xg)/f(Xg)$$

where S_m is a scale factor concerning to a change in mass of T from m_T to $m_{T'}$ an S (Xg) is a transformation factor for the SAF when the adult phantom is tran figured to a corresponding phantom of the individual by scale factors selected sep rately for the head section trunk section and leg section of the adult phanto (SNYDER et coll 1971) Considering the importance of the trunk section a sca factor of the trunk section is used and denoted ε From the definition of SAF S (Xg) is a ratio of two mean values $\overline{\Phi'(X')}$ and $\overline{\Phi(X)}$ of the point specific absorbe fraction $\Phi(X)$ which are defined in the individual and the adult phantom, respectivel $\overline{\Phi(X)}$ is the mean value of the point specific absorbed fraction for all pairs of poi in S and T and $\overline{\Phi'(X')}$ is one for all pairs of points in S' and T' The method based on the assumption that $\Phi(X)$ can be expressed as a function $f(Xe)$ where th effective distance Xg is defined for every S-T pair in the adult phantom In th

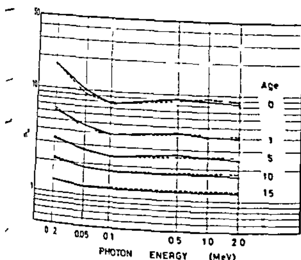


Fig 3 Transformation estimates of S (Xg) compared with Monte Carlo estimates (Snyder et coll 1972) Source and target organ is the total body —— Monte Carlo estimates --- transformation estimates

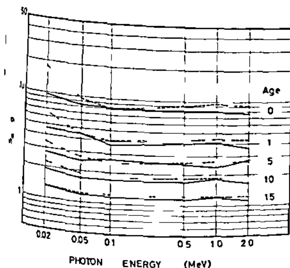


Fig 4 Transformation estimates of S (Xg) compared with Monte Carlo estimates (Snyder et coll 1973) Source and target organ is the ovaries —— Monte Carlo estimates - - transformation estimates

(i) The dose effective distance Xg is determined from the MIRD adult SAF $\Phi(T \leftarrow S)$ by using the graph of $\Phi_{ph}(X)$ as

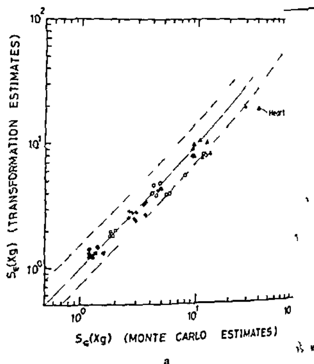
$$\Phi_{ph}(Xg) = \Phi(T \leftarrow S) \tag{12}$$

(ii) $\Phi_{ph}(\varepsilon\ Xg)$ is read on the same graph that is the S (Xg) becomes

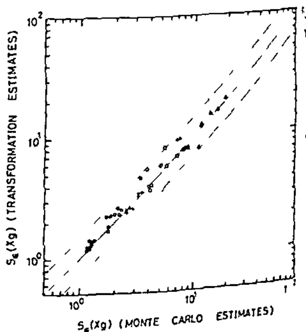
$$S\,(Xg) = \Phi_{ph}(\varepsilon\ Xg)/\Phi_{ph}(Xg) \tag{13}$$

(iii) the SAF for the individual is obtained by

$$\Phi\,(T \leftarrow S\,) = \Phi_{ph}(\varepsilon\ Xg) \tag{14}$$



a



b

Fig 5 Transformation estimates of S (Xg) compared with Monte Carlo estimates (Snyder et coll 1973) Source organ is the ovaries target organs of interest are not these shown but these are the cases where a comparison is possible Symbols ● − ○ and ⌣ show S (Xg) corresponding to 15 10 5 1 and 0-year old phantoms respectively R = S (Xg)$_t$/S (Xg)$_c$ where S (Xg) and S (Xg)$_c$ are the two corresponding estimates --- R = 2 — — R 1 5 —— R 1 — —R 0 7 R 0 5 Photon energies are (a) 1 0 (b) 0 1 and (c) 0 02 MeV respectively

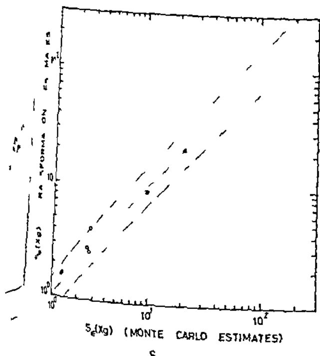


Fig 5 (For legend see opposite page)

It is a basic assumption that characteristics of SAF come from geometrical constitution between S and T and the way of energy deposition in T from scattering photons can be evaluated by Xg on a coordinate system of $\Phi_{pb}(X)$. The present method appears to be more flexible than the previous one since Xg can be determined whenever a MIRD adult SAF is available

Scale factors

Little information exists about the correlation between S–T distance of an individual and his observable physical constitution If it is assumed that it may be more reasonable to consider effects of width and thickness for the individual into the scale factor ε

$$\varepsilon = (\varepsilon \;\; \varepsilon_b \;\; \varepsilon)^{1/3} \tag{15}$$

where ε = trunk width of the individual (cm)/40 cm
ε_b = trunk thickness of the individual (cm)/20 cm
ε = trunk length of the individual (cm)/70 cm

Eq (15) was suggested from eq (10)

The mass scale factor was assumed as follows

$$S_m = \frac{\text{mass of the individual in kg}}{\text{mass of the adult phantom (70 kg)}} \tag{16}$$

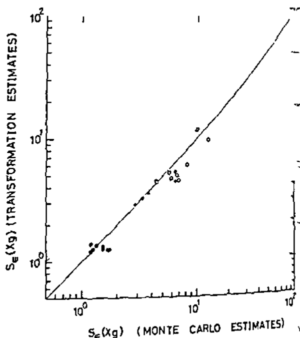


Fig 6 Transformation estimates of $S_\epsilon(Xg)$ compared with Monte Carlo estimates (Hwang et coll 1976 and Jones et coll 1976) Source organ is the liver target organs of interest are not these shown but these are the cases where a comparison is possible Symbols ● + and ○ show S (Xg) corresponding to 15 5 and 1 year old phantoms respectively R = S $(Xg)_1$/ $S_\epsilon(Xg)_2$ where $S_\epsilon(Xg)_1$ and $S_\epsilon(Xg)_2$ are the corresponding estimates ---- R = 2 —— R = 1 and R = 0 5 Photon energy is 0 14 MeV

Results and Discussion

For the case where T is equal to S the AF for total body and the ovaries are shown as examples in Figs 3 and 4 The solid lines show the ORNL results of S (Xg) (SNYDER et coll 1972 SNYDER & FORD 1973) and the dashed lines the present ones For the total body they are in good agreement although the total body is far heavier than the flat ellipsoids For the ovaries the agreement at 0 0? MeV becomes worse as the age decreases It may be due to the contribution of photons scattered from the medium outside the ovaries The fraction of the scattered photons contribution to total absorbed dose may be roughly proportional to the ratio of area of surface to volume of the organ for low photon energies Therefore similar discrepancy at low photon energies may occur for the organs of which ratio of the area of surface to volume is relatively high and which are surrounded by relatively thick medium However the accuracy of the estimates for those organs are expected to be even better than that of agreement within a factor of 2 since the ovaries can be considered as an extreme case the volume of it is the smallest Other examples appear in Fig 1 The values of q (Fig 2) show that the inverse square law holds approximately for photon energy of 0 04 MeV and above but does not hold for photon energy below 0 03 MeV This agrees with the observation for the lunes obtained by HILYER et coll (1972) The value of q is not applicable to the skeleton

Results on the transformation factor where T is different from S are plotted in Fig 5 for photons of energies 1 0 0 1 and 0 02 MeV when the ovary is the source organ The position of each point is determined by the two estimates of S (Xg) that

is the abscissa represents the estimate by the ORNL Monte Carlo method and the ordinate represents the one from the present method When the points are on the line, the two estimates are equal As a whole they are in good agreement although the present method slightly overestimates the SAF of younger ages as energy decreases. When $^{99}Tc^{m}$ is used and the liver is the source organ the result is plotted in Fig. 6 The agreement is not as good as in the ovary case It may be due to the fact that the liver is geometrically more complicated and is nearer to the surface of the body than the ovary However the present method is found to supply the estimates for younger ages within a factor of 2 of the values calculated by the Monte Carlo method

When T is an extended organ such as the total body the total skin or the total skeleton it is necessary to consider energy deposition in a part of T Although those considerations make the method rather complicated some empirical experiences facilitate (YAMAGUCHI 1978)

When the source organ is the total body the SAF for younger ages has been reported (HILYER et coll 1973) Therefore the SAF for the individual can be estimated by an interpolation of the ORNL SAF Eq (11) and the values of q are useful for the interpolation except for T being the skeleton since self absorption is generally a major contribution to those SAF

In practice it is sufficient to carry out the transformation at a representative photon energy instead of every photon energy The value of q is almost the same for 0 1 MeV and above and changes for energy below 0 1 MeV $\Phi_{ph}(X)$ has a similar shape for energy of 0 1 MeV and above and considerably different shapes for energy below 0 1 MeV When a nuclide also emits many gamma rays two average energies are obtained these are over gamma rays of energy above or below 0 1 MeV The representative energies are the energies near those average energies This grouping method of gamma rays especially for energy below 0 1 MeV remains as a problem The publication (ORNL 5000 SNYDER et coll 1974) is available for a transformation calculation since it provides the newest complete data of the adult SAF for 12 mono energies

Conclusions

The present method can estimate SAF of an individual from only present available data a complete set of adult SAF the values of q and the graphs of $\Phi_{ph}(X)$ The accuracy of the estimates is within a factor of 2 of values reliably estimated by the Monte Carlo calculation which is about the same as for the previously published method

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SUMMARY

A transformation method is proposed and used for application of MIRD specific absorbed fractions to various physiques The results are compared with data calculated by SNYDER et coll (1972) for younger persons at photon energies from 0 02 to 2 0 MeV

ZUSAMMENFASSUNG

Eine Transformationsmethode wird vorgeschlagen und zur Anwendung von MIRD-spezifischen absorbierten Fraktionen fur verschiedene Korperbeschaffenheiten verwendet Die Ergebnisse werden mit den von SNYDER et coll (1972) kalkulierten Daten fur jungere Personen bei Photonenergien zwischen 0 02 und 2 0 MeV verglichen

RESUME

L auteur propose une methode de transformation et l utilise pour l application des fractions absorbees spécifiques de MIRD à differentes conditions physiques Il compare les resultats avec les donnees calculees par Snyder et coll (1972) pour des personnes plus jeunes à des energies de photons de 0 02 a 2 0 MeV

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FROM THE DEPARTMENT OF HOSPITAL PHYSICS (DIRECTOR R WALSTAM) AND THE DEPARTMENT OF GYNAECOLOGIC ONCOLOGY (DIRECTOR B TJERNBERG) RADIUMHEMMET, KAROLINSKA SJUKHUSET, S 104 01 STOCKHOLM SWEDEN

DOSE DISTRIBUTION IN 42 MV ROENTGEN IRRADIATION OF CERVICAL CARCINOMA

B FORSBERG I LAX and NINA EINHORN

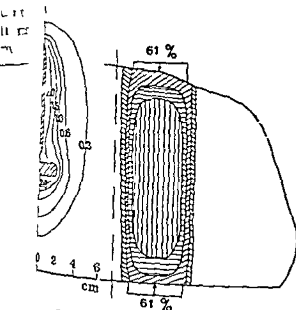
The technique of irradiation of carcinoma of the uterine cervix is determined by the size and position of the primary tumour and the regional routes of spread particularly to the pelvic nodes In order to obtain a suitable dose distribution a combination of intracavitary and external irradiation is necessary in most cases Difficulties exist in achieving the optimum dose distribution in the tumour and lymph node areas without giving unacceptably high doses to the surrounding tissues the bladder and rectum being the most critical

Several reports have appeared on a combination of external and intracavitary irradiation (TRANTER 1959 RANUDD 1960 BLOMFIELD 1961 JONES et coll 1972 GLAZEBROOK 1974 JOHNSSON & NORDBERG 1975) Most of these reports discuss the problems when irradiation with ^{60}Co or a linear accelerator is applied

Special shielding blocks have been designed for the external irradiation with 42 MV roentgen rays and the distribution of the absorbed dose and the Cumulative Radiation Effect (CRE) (KIRK et coll 1971) has been determined and compared with the previous multiple beam technique

Intracavitary irradiation The Stockholm technique for the intracavitary irradiation of gynaecologic malignant tumours has been presented by HEYMAN (1929) WALSTAM (1954) KOTTMEIER & WALSTAM (1963) and KOTTMEIER (1964)

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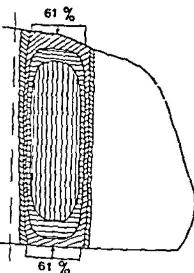


Fig. 1

Fig 2

Fig. 1 Isodose rates (Gy h) for a common applicator The intrauterine applicator is loaded with 70 mg ²²⁶Ra and the vaginal applicator with 71 mg.

Fig 2. Half of the symmetric relative dose distribution for 42 MV roentgen rays, delivered with 2 anterior and 2 posterior beams Approximately 15 of the parametrial dose is obtained in the central pelvic tissues Beam separation 4 cm and beam width 6 cm ☐ 95–105 ☐ 85–95 ☐ 65–85 ☐ 35–65 ☐ 35

In the irradiation of stages I B II A and II B one intrauterine and one vaginal applicator, loaded with about 70 mg ²²⁶Ra each are generally used (Fig 1) Two irradiations of 20 to 30 hours duration are given with an interval of about 3 weeks Two to three weeks after the second intracavitary irradiation a supplementary external irradiation is given resulting in a total dose to the parametrium of 50 to 55 Gy

The dose to the posterior bladder wall and the anterior rectum wall at intracavitary irradiation is usually in the range of 25 to 40 Gy The limit for the total dose that can be given with this fractionation is considered to be 55 Gy to the bladder wall and 45 Gy to the rectum wall Therefore during the external irradiation of the lymph nodes an additional dose can be administered to the central part of the pelvis the amount depending on the dose previously achieved by the intracavitary irradiation

External irradiation Since 1968 a 42 MeV betatron has been used It has an advantageous depth dose distribution and reduced integral dose as compared with ⁶⁰Co therapy for opposing beam techniques With the betatron a multiple beam technique was applied and depending on the dose previously given to the walls of the bladder and rectum at the intracavitary irradiation 4 to 6 beams were used (Fig 2) The dose to the bladder and rectum could to a certain extent be varied by using different weighting on the beams

The disadvantages of the multiple beam technique were (1) a low dose to the central areas situated cranially to the uterus where the presacral lymph nodes are

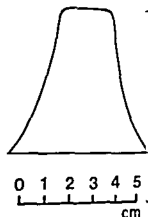


Fig 3 Cross section of the shielding block made of Wood s metal

located (2) no possibility of protecting the groin regions and of shielding the upper lateral corners of the fields (where no lymph nodes of interest are located (3) limited accuracy in the positioning of the small beams during irradiation and (4) many setting up procedures prolonging the treatment time

In order to improve the technique the betatron was supplied with a holder for shielding blocks The block made of Wood s metal was placed free in air with minimum distance to the beam diaphragm The width of the shielding block was designed to give maximum shielding up to 1 cm laterally and a full unatteanuated dose to points at greater distances than 5 cm from the middle line Further the shape aimed to compensate the decrease in the dose from the intracavitary irradiation laterally by a gradually increasing dose from the external irradiation (Fig 3)

Dose distribution was determined in 2 transverse planes and one frontal plane at 10 cm depth in a water phantom with an automatic isodose plotter (RFA I Scanditronix Uppsala Sweden) The depth doses were also checked with a thimble ionization chamber in a polystyrene phantom (Figs 4-6)

The total dose i e the dose from both the intracavitary and the external irradiation in a lateral direction from the midline at 10 cm depth appears in Fig 7 The intracavitary irradiation is assumed to be 6 000 7 000 and 8 000 mgh respectively This is the range of mgh most common in clinical routine work for example 7 000 mgh is obtained with applicators loaded with 140 mg (70 + 70) and 2 irradiations each of 25 h duration The dose from the external irradiation is assumed to be 40 Gy to the parametrium

All the calculations of the absorbed doses and CRE are made along a line through the so-called points A and B (MEREDITH 1967)

One problem in the conventional intracavitary therapy with radium applicators is the movement of the applicators during irradiation (JOELSSON & BACKSTRÖM 1969 JOHNSSON & NORDBERG 1973) Mechanical constructions reduce this problem to some degree but reduce the flexibility and individualization of the system

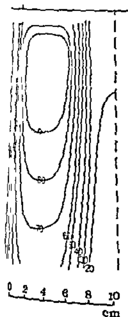


Fig. 4

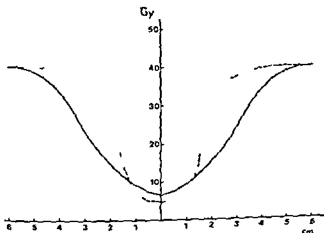


Fig. 5

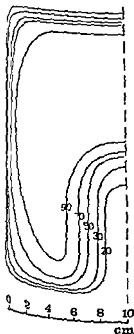


Fig. 6

Fig. 4 Half of the symmetric iso dose diagram for 42 MV roentgen rays with shielding block. Beam size 18 cm × 18 cm. SSD 170 cm.

Fig. 5 Beam profile at 10 cm depth — Shielding block technique – – Four field technique.

Fig. 6 Relative isodose distribution in a plane at 10 cm depth.

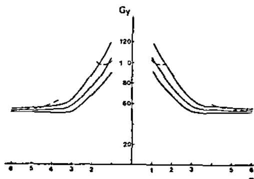
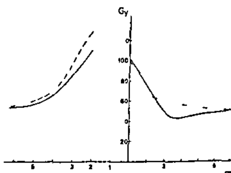



Fig 7

Fig 8

Fig 7 Dose profile laterally thorough points A and B —— Total dose with an intracavitary treatment of 6 000 7 000 and 8 000 mgh respectively and an external irradiation with the shielding block technique --- Total dose with an intracavitary irradiation of 7 000 mgh and an external irradiation with the four field technique

Fig 8 Dose profile with the 2 external irradiation techniques The dose distribution in lateral direction when the applicators (7 000 mgh) are displaced 1 cm laterally to simulate a displacement of the uterus —— Shielding block technique --- Four field technique

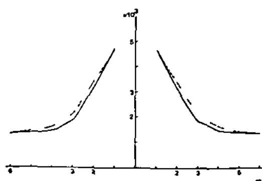
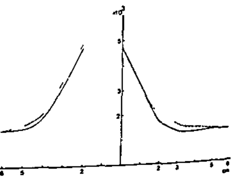



Fig 9

Fig 10

Fig 9 Calculated CRE values for the total irradiation The intracavitary irradiation is 7 000 mgh —— Shielding block technique --- Four field technique

Fig 10 Calculated CRE values for the total irradiation with a simulated displacement of the uterus of 1 cm The intracavitary irradiation is assumed to be 7 000 mgh —— Shielding block technique, --- Four field technique

Another factor likely to influence the planned dose distribution is the difficulty of adjusting the external radiation beams to exactly the same position throughout the treatment period

By displacing the applicators 1 cm laterally a displacement of the uterus is simulated (JOHNSSON & NORDBERG 1975) The effect on the dose distribution is shown in Fig 8

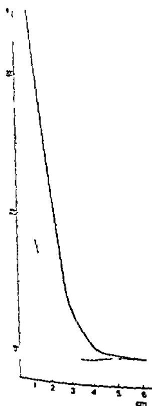


Fig. 11. Relative CRE values laterally (——) and relative total dose (----). The point of normalization is 6 cm laterally. The intracavitary irradiation is assumed to be 7 000 mgh. Shielding block technique.

Biologic effect. The intracavitary irradiation is given with a low dose rate and the external irradiation is divided into several fractions with a high dose rate. In the calculations for the design of the shielding block these differences in the dose rates have not been considered.

The validity of simply summing the absorbed doses, regardless of the dose rates, was estimated by calculating the biologic effect using a mathematical model. Several mathematical models on the dose-effect relationship in radiation therapy have been presented (COHEN 1968, ELLIS 1969, KIRK et coll. 1971, 1972, 1973, 1975). The KIRK model (CRE) seems to be the one most in use in Sweden and was therefore used (cf. TURESSON 1978). For the calculations an RBE value of 0.87 (KIRK et coll. 1972) was chosen for 42 MV roentgen rays. The factor for the volume correction was taken as unity, as the calculated CRE values were compared for different schedules (KIRK et coll. 1975). A gap correction according to KIRK et coll. (1975) was applied. The CRE calculations were performed for different situations (Figs 9–11).

Discussion

A comparison between the dose distribution from the new and the previous external irradiation techniques, with no displacement of the applicators from their

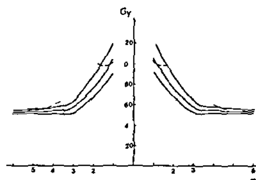


Fig 7

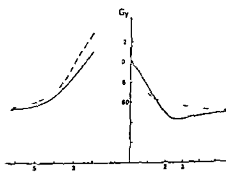


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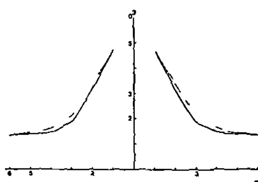


Fig 9

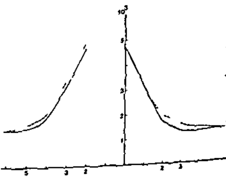


Fig 10

Fig 9 Calculated CRE values for the total irradiation The intracavitary irradiation is 7 000 m *—— Shielding block technique --- Four field technique*

Fig 10 Calculated CRE values for the total irradiation with a simulated displacement of the uter of 1 cm The intracavitary irradiation is assumed to be 7 000 mgh —— Shielding block techniq --- Four field technique

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BRONCHIAL ARTERY INFUSION OF MITOMYCIN-C IN ADVANCED BRONCHOGENIC CARCINOMA

C HELLEKANT and L SVANBERG

The prognosis of inoperable pulmonary carcinoma is poor Radiation therapy is (Fue) ... although some prolongation of survival may be obtained (ROSWIT et ... 1968) Conflicting opinions exist about the value of combined cytostatic and ...ion therapy but improved results have been reported (CHAN et coll 1976) The experiences at this hospital indicate that combined preoperative bleomycin and radiation therapy can increase the number of patients suitable for excisional surgery ... improve survival rates (SVANBERG 1976) Although several cytotoxic agents with ... response rate of approximately 20 per cent are available (WASSERMAN et coll 1975) very little success has been achieved either in terms of palliation or in prolongation of survival (LIVINGSTON 1977)

The best effect has been obtained with polychemotherapy such as COMB (cyclophosphamide oncovin methyl CCNU and bleomycin) and BACON (bleomycin adriamycin, CCNU oncovin and nitrogen mustard) (LIVINGSTON et coll 1975 1976) The drawback of systemically administered chemotherapy is that all effective ...s developed produce major side effects contributing to the patient s death in 3 to 5 per cent and shortening survival in perhaps another 10 per cent (LIVINGSTON) Therefore for increasing the concentration of the drug in the tumor and decreasing ... the rest of the body it seems logical to infuse the drug directly into the tumor feeding bronchial artery

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The experiences with preoperative selective intraarterial infusion of mitomycin (MMC) in patients with squamous cell carcinoma of the lung clinical stage II have been reported previously (HELLEKANT et coll 1978) In this communication the results in patients with primarily inoperable squamous cell carcinoma or adenocarcinoma of the lung are reported

Material and Methods

The material comprised 17 patients with primary pulmonary carcinoma 13 with squamous cell carcinoma and 4 with adenocarcinoma All were men except two in the adenocarcinoma group The median age at the time of diagnosis was 61 years (range 45–75)

Before treatment all patients were evaluated with physical examination routine blood analyses with liver function tests ECG spirometry and ^{133}Xe spirometry (MIÖRNER 1968 SVANBERG 1972) The extent of the primary tumor was estimated with chest radiography bronchoscopy and mediastinoscopy and in 8 cases also with pulmonary angiography The patients were classified and staged according to the TNM classification (UICC 1974)

When clinically indicated scintigraphy of the skeleton liver or brain was performed

All patients were classified as stage III except 2 with squamous cell carcinoma who belonged to stage II They were both considered inoperable due to recent myocardial infarction and severe asthma respectively

Selective bronchial angiography was performed according to a technique described by BOTENGA (1970) and HELLEKANT (to be published)

The size of the tumor and its vascularization were estimated from the films which were also scrutinized for the presence of a spinal artery

Following angiography in a p and lateral projection 10 mg of MMC diluted in 100 ml of physiologic saline was infused into the proper bronchial artery at a rate of 6 ml/min

One patient received only MMC while the other 16 received in addition vincristine (VCR) intravenously with or without combination with bleomycin (BLM) intramuscularly (Table) Different schedules were used but the amount of MMC given at each arterial infusion was 10 mg and the total amount of BLM used at each course was fairly equal

BLM was given either in three doses of 5 to 10 mg given the day before the same day and the day after angiography or in doses of 5 mg given 6 consecutive days before the angiography VCR was given 6 hours before BLM or MMC respectively Eight patients were given one course of intraarterial MMC three received 2 three received 3 one received 4 and two received 5 courses

The interval between the courses varied between 1 and 16 weeks (median 3 weeks) the longer intervals being used when multiple courses were given

The effect of the therapy was evaluated by means of clinical examination repeated chest films spirometry and ¹³³Xe spirometry Repeat bronchoscopy was performed in [illegible] The evaluation was performed before any additional treatment was [illegible] Thrombocytes and white blood cells were controlled in all patients once a week after the infusion

The definitions of objective response for measurable lesions on chest films were complete remission = no evidence of tumor partial remission = more than 50 per cent reduction of the product of the two largest perpendicular tumor diameters

For non measurable but evaluable lesions an unequivocal marked regression of tumor mass or atelectasis was considered an objective response

At bronchoscopy disappearance or marked regression of exophytic tumor estimated as more than 50 per cent or a marked reduction of bronchus compression was considered an objective response

All other findings at chest radiography and bronchoscopy in the absence of progressive disease were designated no change

Six patients were operated upon 26 to 73 days after the first infusion (median 38 days) pneumonectomy in 2 lobectomy in one and exploratory thoracotomy in 3 The operations were considered radical in 2 patients The others as well as patients who did not respond or who relapsed received complementary treatment with chemotherapy irradiation or both combined

Results

The effect of the therapy appears in the Table

An objective tumor regression as registered with chest radiography or bronchoscopy was observed in 11 of 17 patients In 3 of these (Nos 4 11 14) a partial remission and in 8 (Nos 2 5 6 7 9 10 12 15) a marked regression was achieved

The median survival was 33 weeks (range 12 to 71 + weeks)

On chest films partial remission was evident in 3 patients (Nos 4 11 14) and marked regression in 7 (Nos 2 6 7 9 10 12, 15) The appearances on chest films were unchanged in 6 patients in one progression had occurred (No 16) At bronchoscopy marked regression was found in 4 (Nos 2 5 10 14) and no change in 4 patients (Nos 1 6 13 15) In 9 patients the examination was not repeated

Among 6 patients with unchanged chest films bronchoscopy revealed a marked regression in one (No 5)

The physiologic condition as measured with spirometry and ¹³³Xe spirometry was improved in 2 patients (Nos 2 14) who also had regression of tumor size on chest films and at bronchoscopy The condition was unchanged in 11 patients and improved in one (No 1) whose tumorous lung lobe was already totally atelectatic at the start of chemotherapy In 3 patients the examinations were not repeated

Six patients (Nos 1–6) all belonging to stage III were operated upon The clinical classification proved to be correct in 5 of these

The experiences with preoperative selective intraarterial infusion of mitomycin C (MMC) in patients with squamous cell carcinoma of the lung clinical stage II have been reported previously (HELLEKANT et coll 1978) In this communication the results in patients with primarily inoperable squamous cell carcinoma or adenocarcinoma of the lung are reported

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Table (*cont*)

P L ne	Later com lementary tra ment	Survival (weeks) (-) = alive	Type of op Interval (days) Surgical TNM	Comments
	VCR, BLM R	35	E 29 T3N_M0	Metastases at autops
	—	40	P 38 T2N1M0	Metastases at autops
	VCR BLM R	71(-)	E 26 T3N1M0	
	—	34(-)	L 42 T2N0M1	Metastasis in the resected lobe
	—	13	E 73 T3N1M0	Died of hem ptysis 3 w postop
	5FU CCNU	16	P 41 T3N1M1	Only half of tumor perfused
	5FU BLM A, R	31		Metastases at autopsy
	5FU C, MTX, R	39		Sup sulcus tumor supplied also from subclavian artery
	VCR, C A MTX, R	39		Metastases at autops
	—	21		Died of status asthmaticus bleeding ulcer
	—	19		Metastases at autopsy
	—	12		Died of myocardial infarction no autops earlier m ocardial infarcti n
	VCR, BLM R	4_		Metastases no autopsy
	—	58(-)		Large tumor with metastases to the same lung li es at home no s mptoms
	BLM R	31		Mediastinal growth diagnosed at pulmonary angiograph
	VCR, BLM R	8		Metastases at autops
	VCR BLM R	33		Metastases at autopsy

Change in physiologic stage improved = impaired unchanged - not repeated VCR = vincristine, BLM = bleomycin MMC = mitomycin C 5FU 5-fluorouracil CCNU chloroethyl cyclohexyl nitrosourea C = cyclophosphamide MTX methotrexate A adriamycin, R irradiation, E = exploration, P = pneumonectomy L - lobectomy

other 3 died 3 11 and 31 weeks after surgery In one patient the clinical stage III was reduced to stage II at surgery (No 2) A previously observed tumor in the left main bronchus had disappeared after chemotherapy permitting a radical pneumonectomy to be performed The patient was given no further therapy and died 34 weeks later with massive metastases

Only one of the non-operated patients is alive A 69 year-old man (No 14) had a la e tumor and metastases in the right lung (Fig 2 a, b) Bronchoscopy revealed occlusion of the bronchus in the right lower lobe and a biopsy demonstrated poorly differentiated squamous cell carcinoma The patient was considered inoperable due to severely impaired lung function

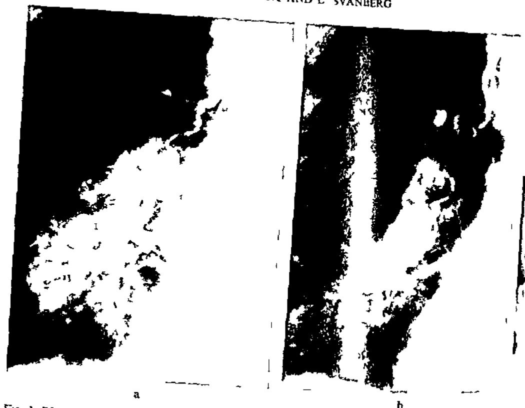


Fig 1 75 year-old man *with squamous* cell carcinoma in the right lower lobe a) Bronchial angiography Richly vascularized *tumor* The patient received 3 intraarterial infusions of 10 mg mitomycin C b) Repeat angiography in connection with third intraarterial infusion of mitomycin C Partial remission of tumor

At bronchial angiography a richly vascularized tumor was demonstrated (Fig 2c) The patient received 5 courses of intraarterial MMC during a period of 5 months without side effects and the tumor regressed to approximately one third of its original volume (Fig 3) The patient is alive and feels well 14 months after start of chemotherapy and has not been given further treatment The tumor is observed continuously and has remained stable for 8 months Repeat bronchoscopy one year after the first infusion demonstrated a marked regression and at repeat spirometry the function of the right lung had improved considerably

Two patients classified as stage II but inoperable due to severe asthma and previous myocardial infarctions respectively both succumbed to recurrence of these diseases 21 and 12 weeks after start of treatment Five courses of MMC had been administered to the one and 3 to the other Both responded with regression of tumor size on chest films and in one bronchoscopy showed a marked regression Autopsy was not performed

All the others died of their malignant tumors 19 to 42 weeks after start of chemotherapy

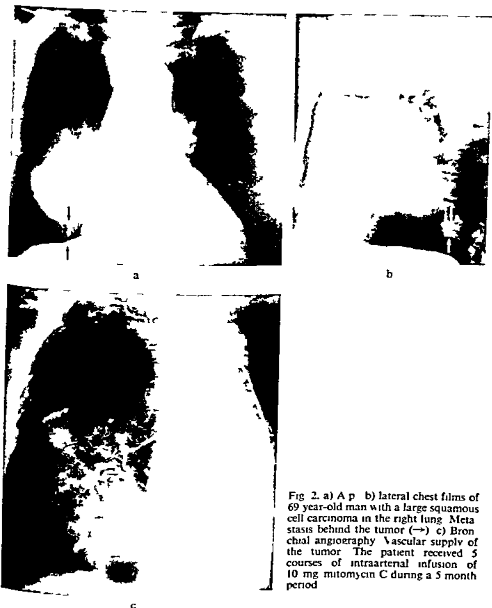


Fig 2. a) A p b) lateral chest films of 69 year-old man with a large squamous cell carcinoma in the right lung Metastasis behind the tumor (→) c) Bronchial angiography Vascular supply of the tumor The patient received 5 courses of intraarterial infusion of 10 mg mitomycin C during a 5 month period

Side effects All patients experienced a burning sensation in the chest or in the dorsal muscles during angiography Except for coughing in a couple of patients n side effects were observed during the infusion of MMC but in many cases a fever occurred the day after the infusion Some patients also had a moderate In one patient who received 5 courses with a total of 5 mg of VCR 120 m and 50 mg of MMC a transient alopecia developed (No 10)

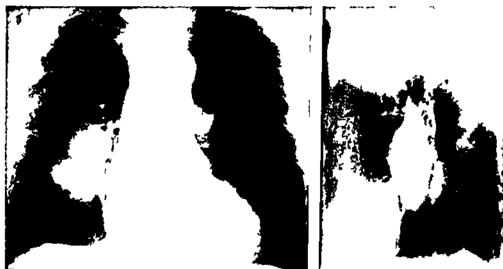


Fig 3 Same case as in Fig 2 Chest films 7 months after beginning of intraarterial chemotherapy Tumor has regressed to approximately one third of original volume

Chemical pneumonitis was encountered in 2 patients (Nos 10 and 12) and in one of them a 72 year old man with extensive atheromatosis the infusion therapy was discontinued due to thrombosis of one of his external iliac arteries The other patient received 4 more courses without local side effects In both patients the pneumonia resolved rapidly

In a third patient (No 7) a small extravasation of contrast medium to the mediastinum occurred at bronchial angiography 6 weeks after previous infusion of MMC and the catheter was immediately withdrawn The patient developed a burning pain in the mediastinum lasting for 24 hours but no further symptoms occurred Repeated chest films did not reveal any additional pathology At repeat angiography 10 days later the bronchial artery was occluded and the therapy therefore discontinued

No neurologic symptoms or signs of hematopoietic toxicity were registered

Discussion

The concept of treating bronchial carcinoma with selective infusion of a cytostatic drug directly into the tumor feeding artery is not new It was tried with different drugs during the sixties (BOIJSEN et coll 1964 KAHN et coll 1965 HALLER et coll 1966 NORDENSTRÖM 1966 TATE & VIAMONTE 1968 WIRTANEN & ANSFIELD 1968) but the method was abandoned partly because of poor results partly because of major complications such as transverse myelitis aortic rupture and ulcerations of the esophagus and trachea (FEIGELSON & RAVIN 1965 RHEINLANDER et coll 1 DI CHIRO et coll 1967 STECKEL et coll 1967 REMY et coll 1968)

Since December 1975 more than 70 bronchial angiographies have at this hospital and cytotoxic drugs (MMC BLM and adriamycin) inj

bronchial arteries in more than 40 patients Apart from the side effects reported in the present communication no complications have occurred Therefore the method seems to be reasonably safe when a meticulous angiographic technique is used and the drug properly diluted

In the present series of advanced pulmonary carcinoma an objective response was achieved in 11 of 17 patients This figure corresponds favourably with figures on record for systematically administered chemotherapy in advanced non oat cell carcinoma (VINCENT et coll 1975 HANSEN et coll 1976)

Intraarterial chemotherapy is still practiced in Japan (OGATA 1975 personal communication) but only one publication on the subject has been found (NEYAZAKI et coll 1969) Their material included 15 patients with adenocarcinoma and 5 with squamous cell carcinoma The patients were treated between 1 and 4 times with 10 mg of MMC diluted in saline and the overall response rate was 66 per cent for adenocarcinoma and 25 per cent for squamous cell carcinoma However a closer comparison with the present results is not possible since NEYAZAKI et coll did not include any information on the tumor stages The high resection rate (13/20) implies that many tumors were of limited extent In the present series only 2 of 17 tumors could be radically resected and all patients with adenocarcinoma already had distant metastases at the time of diagnosis

Previously HELLEKANT et coll have reported experiences with preoperative intraarterial infusion of MMC in 9 patients with clinically stage I–II squamous cell carcinoma In that preliminary report a complete remission of the tumor confirmed at subsequent surgery was achieved in 2 patients and a partial remission in another after a single infusion of 10 mg of MMC Later VCR (intravenously) and BLM (intramuscularly) were added which are believed to potentiate the effect of MMC (POUILLART et coll 1974 TERASIMA et coll 1977 MIYAMATO et coll 1977)

In the present series all but 2 patients (Nos 4 17) received small doses of VCR and BLM or BLM only for the same purpose but the experience is still too limited to permit any definite conclusions on the value of such additional synchronizing chemotherapy However the combination of BLM and MMC appears to have a more favourable effect on larger tumors especially if poorly differentiated while smaller tumors may regress completely without pretreatment with BLM

In accordance with NEYAZAKI et coll and OGATA (1977) repeated infusions were found to be more effective than single ones especially in larger tumors

In several cases where the angiography was repeated a markedly diminished tumor vascularity after previous intraarterial chemotherapy was demonstrated This was true especially in responding tumors and probably caused by tumor necrosis and shrinkage The same has been observed following radiation therapy (NEWTON & PREGER 1965)

MMC has a strong anti tumor effect confirmed both experimentally and clinically but the drug is rapidly inactivated in the liver spleen kidneys brain and heart (FUJITA 1971) When intravenously administered it must therefore be given in large

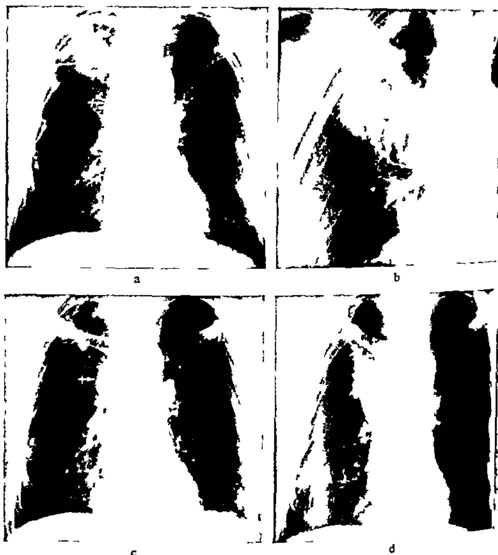


Fig 4 a) Chest film of 52 year old man with a 5 cm in diameter squamous cell carcinoma in th right upper lobe (→) Evidence of mediastinal metastases (↔) b) Bronchial angiography Vascula supply of tumor The patient received 3 courses of intraarterial mitomycin C with an interval o 3 and 4 weeks c) Chest film 69 days after beginning of intraarterial chemotherapy The tumor ir the parenchyma has regressed markedly (→) Mediastinal metastases somewhat more evident (↔) d) Chest film 110 days after beginning of intraarterial chemotherapy The parenchymal tumor barel visible Marked progression of mediastinal metastases which were not perfused by mitomycin-C

doses to be effective This increases the risk of systemic toxicity especially myelo suppression

In a survey of the Japanese literature FRANK & OSTERBERG (1960) concluded tha in 67 per cent of responding and in 40 per cent of non responding patients hemato poietic toxicity occurred after intravenous administration of MMC The toxicity wa directly related to the dose and rarely occurred below a total amount of 40 mg

Most of the present patients received 10 to 30 mg of MMC but as much as 50 mg was given to 2 patients without hematopoietic side effects. An interval of 3 weeks between the courses has been suggested for minimizing myelosuppression (FRANK & OSTERBERG). In the present series the intervals were often longer particularly when multiple courses were given.

The drawback of selective intraarterial chemotherapy is that it is strictly local and does not affect regional or distant spread of the disease. This will be exemplified by the following case. A 52-year-old man (No. 11) had on admission a 5 cm in diameter poorly differentiated squamous cell carcinoma in the right upper lobe (Fig. 4 a). No abnormality was found at mediastinoscopy despite radiographic suggestions of mediastinal metastases. Bronchial angiography demonstrated a fairly richly vascularized tumor (Fig. 4 b) and the patient was given 3 courses of intraarterial MMC at intervals of 3 and 4 weeks. The tumor in the parenchyma almost completely disappeared and the mediastinal nodes were stable or possibly even somewhat less evident (Fig. 4 c). Unfortunately the patient had an attack of acute thromboembolism and the therapy had to be discontinued. Three weeks later the mediastinal metastases had grown a little but 4 weeks later they had increased markedly while the parenchymal tumor was stable (Fig. 4 d). The patient died shortly thereafter and at autopsy only a small remainder of the primary tumor was found. An 8 cm metastasis was confirmed in the mediastinum.

SUMMARY

Bronchial angiography was performed in 17 patients with advanced non-oat cell bronchogenic carcinoma The patients were treated 1 to 5 times with infusions of 10 mg of mitomycin-C (MMC) into the tumor feeding bronchial artery All but 2 patients received in addition small doses of vincristine (intravenously) and bleomycin (intramuscularly) or only bleomycin to potentiate the effect of MMC No major side effects occurred and the systemic toxicity was insignificant An objective tumor response was encountered in 11/17 patients Intraarterial chemotherapy is strictly local and therefore effective especially in patients with limited or locally advanced disease In patients with more extensive disease an adjunctive therapy of a more regional or systemic modality must be given

ZUSAMMENFASSUNG

Eine bronchiale Angiographie wurde bei 17 Patienten mit vorgeschrittenen nicht-Oat Zell bronchogenem Karzinom vorgenommen Die Patienten wurden 1 bis 5 mal mit Infusion von 10 mg Mitomycin C (MMC) in die Tumor versorgende Bronchial Arterie infundiert. Alle ausser 2 Patienten erhielten zusatzlich kleine Dosen von Vincristin (intravenos) und Bleomycin (intramuskular) oder nur Bleomycin um den Effekt von MMC zu verstarken Keine grosseren Nebeneffekte traten auf und die generelle Toxizitat war unbedeutend Eine objektive Tumor Respons wurde bei 11/17 Patienten erreicht Die intraarterielle Chemotherapie ist strikt lokal und deshalb besonders effektiv bei Patienten mit begrenzter oder lokal vorgeschrittener Erkrankung Bei Patienten mit mehr ausgebreiteter Erkrankung muss eine zusatzliche Therapie von mehr regionaler oder genereller Art verabfolgt werden

RESUME

Une angiographie bronchique a ete faite chez 17 malades atteints de carcinome bronchique avance qui n etait pas du type anaplasique a petites cellules Les malades ont été traites de 1 a 5 fois par des perfusions de 10 mg de Mitomycine C (MMC) dans l artère bronchique nourriciere de la tumeur Tous les malades sauf deux ont reçu en outre des petites doses de Vincristine (par voie intraveineuse) et de Bléomycine (par voie intramusculaire) pour potentialiser l effet de la MMC Il n y a pas eu d effet secondaire important et la toxicite systémique a eté insignifiante On a constaté une reponse objective de la tumeur chez 11 malades sur 17 La chimiothérapie intraartérielle est strictement focale et par consequent efficace specialement chez les malades qui ont une tumeur limitée ou avancée localement Chez les malades qui ont une tumeur plus étendue il faut administrer un traitement complementaire sous une modalite plus régionale ou systemique

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EN BLOC IRRADIATION OF UNRESECTABLE BRONCHOGENIC CARCINOMAS AND THEIR REGIONAL LYMPHATICS

P FLODGREN L BALDETORP T LANDBERG C MERCKE T MÖLLER and G SVAHN TAPPER

Bronchogenic carcinoma has a serious prognosis Once established in the secondary or tertiary bronchial divisions the tumour rapidly invades the lymphatics and the blood vessels resulting in widespread dissemination The ipsilateral hilar and inferior tracheobronchial lymph nodes are involved in approximately 75 per cent of the patients at the time of diagnosis and from there the tumour progresses to the adjacent mediastinal lymph nodes At mediastinoscopy more than 50 per cent of patients have mediastinal involvement (GOLDBERG et coll 1974) Furthermore even in what seems to be limited disease multiple organ involvement is often present with dissemination to the brain and skeleton in approximately 20 per cent and to the liver in about 2 per cent (HANSEN & MUGGIA 1972) Thus even if local control of the primary tumour and its regional nodes is achieved by irradiation many patients will die from distant metastases

Analysis in 1970 in Lund (Fig 1) showed that after conventional roentgen irradiation only one (with pleural deposits left after resection) out of 10 patients survived Further irradiation with ^{60}Co gamma rays using individual multi beam dose planning correction for tis u heterogeneity and repeat controls of absorbed dose by in vivo measurements and delivering about 60 Gy in 6 weeks to the tumour resulted in a

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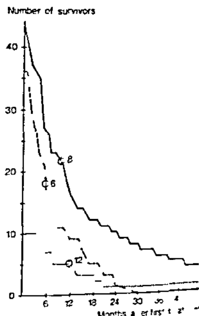


Fig. 1 Results of radiation therapy of unresectable bronchogenic carcinoma in 10 patients irradiated with conventional roentgen (1967) —— 43 with ^{60}Co gamma rays (1967) and - - - 36 with high energy electrons (1966–1968) The median survival (⊕) is given for each treatment technique One year survival was for patients irradiated with conventional roentgen 5 10 with ^{60}Co gamma rays 16 43 (37) and with high energy electrons 9 36 (25)

median survival of only 8 months Treatment with high energy electrons to the same absorbed dose and target volume with fewer fractions gave a median survival inferior to that obtained with ^{60}Co irradiation (LANDBERG et coll 1972) It was considered that the adverse effects of the therapy had been marked and the target volume too small therefore it was decided that from January 1971 patients with unresectable bronchogenic carcinoma should be treated with opposed antero-posterior and postero-anterior beams to include the tumour both hilar regions and the mediastinum from the jugulum downward covering the inferior tracheobronchial nodes In some patients both supraclavicular fossae were also included in the target volume The total target absorbed dose was set at 40 Gy to be given with 2 Gy per fraction as midpoint absorbed dose About half of them were irradiated in one series over 4 weeks and the remaining half in split-course with two series over totally 7 weeks. The two patient series were sequential and not randomized but during the entire period no other major change was introduced in the care of these patients Chemotherapy was not given at the time of the initial treatment

The purpose of the present report is to give a comparison between results and adverse effects of the two regimens

Material and Methods

From January 1971 to January 1975 97 patients with unresectable bronchogenic carcinoma were accepted for irradiation at this department During the first 2 years 52 patients were treated in one series (Group I) and during the second half of the period 45 patients were treated with a split-course regimen (Group II).

Table 1

Distribution of tumour types in the two series

	Number of patients irradiated in	
	one series	two series
Squamous cell carcinoma well to moderately well differentiated	20	15
Squamous cell carcinoma poorly differentiated	22	18
Oat cell carcinoma	6	8
Adenocarcinoma	4	3
Undifferentiated carcinoma	—	1
Total	52	45

Table 2

Reasons for inoperability in 69 patients not subjected to thoracotomy

	Number of patients irradiated in	
	one series	two series
Central growth	4	7
Advanced tumour	16	5
Histology	6	8
Poor general condition of the patient	13	9
Surgery refused by the patient	—	1
Total	39	30

The composition of the two groups with regard to sex and age was as follows Group I—males 49/52 age 46 to 75 (mean 66) years Group II—males 39 45 age 49 to 79 (mean 65)

The pre therapeutic staging and evaluation of operability included a comp ete history and physical examination routine blood analyses with liver function tests ECG chest and bone radiography survey cytologic examination of sputum bronchoscopy with multiple biopsies and mediastinoscopy and in some cases scalene node biopsy In most patients liver scintigraphy was performed as was spirometry When appropriate brain scintigraphy fine needle aspiration biopsy of the liver and pleural effusion cytology were also included

The distribution of the microscopic types did not differ between the 2 groups (Table 1)

In 69 of the 97 patients no thoracotomy had been performed The reasons for inoperability are given in Table 2 Tumour were considered unresectable when tumour growth had been demonstrated le than 2 cm from the carina (central growth) Hilar mediastinal and scalene n de involvement [illegible]

Table 3

Type of surgery in 28 patients

	Number of patients irradiated in	
	one series	two series
Exploration only	8	10
Lobectomy	2	2
Pulmectomy	3	3
Total	13	15

Table 4

Tumour extension in the 97 patients

	Number of patients irradiated in	
	one series	two series
Most distant lymph node metastases		
Hilar lymph nodes	13	15
Mediastinal lymph nodes	24	18
Scalene lymph nodes	4	4
Pleural and chest wall involvement	8	8
Distant metastases	2	—
Remaining tumour in main bronchus after surgery	—	2

from surgery (advanced tumour) Oat cell carcinoma (histology) was considered unresectable Patients with reduced pulmonary function heart disease or other major complicating disease were also excluded from surgery

Thoracotomy was carried out in 28 patients (Table 3) and could be extended to a lobectomy or pulmectomy in 10 but in all these patients microscopy showed that the surgery had not been radical

Thus all 97 patients had residual tumour at the beginning of the irradiation The extension of the disease appears in Table 4 Two patients had distant metastases (vertebral bodies) but in both cases all demonstrated tumour could be included in the target volume No significant difference between the 2 groups was noticed and thus both groups should have the same prognosis

Radiation treatment was given with 2 coaxial opposed equally weighted ^{60}Co beams at SSD 70 cm The patients were irradiated in only the supine position Beam shaping was performed with 5 cm thick lead blocks placed near the collimator Correction for tissue heterogeneity was not performed and therefore the true absorbed dose in the lung tissue was usually in excess of the one calculated on the assumption of homogeneous water-equivalent tissue Beam and contour compensators were not used The point at which the target absorbed dose is stated is on the

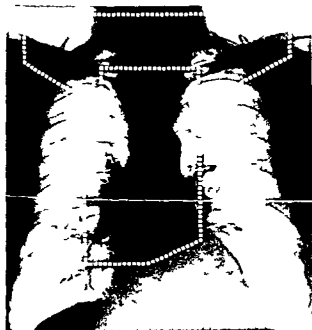


Fig. 2 Arrangement of anterior field in a patient with tumour of the right lung and hilar metastases Included in the target volume are lymph nodes in the inferior tracheobronchial region, left hilar region mediastinum and as an option the supraclavicular fossae

central axis midway between the beam entrances Any substantial variation in target absorbed dose in the cranio caudal direction due to variation in patient outline characteristics was diminished by means of successive reduction of the field size towards the end of irradiation The size and shape of the fields were defined under fluoroscopy and controlled on films The peak absorbed dose in the centre of the beams was always measured and usually also the exit absorbed dose but intra cavitary measurements of absorbed dose were not carried out as a routine

A typical arrangement for the ventral field is given in Fig 2 and the same patient is given the distribution of the absorbed dose in a transversal section in Fig 3

Both fields were treated at each fraction 5 fractions being given weekly An absorbed dose of 2 Gy at the point mentioned was given at each fraction The total target absorbed dose was 40 Gy given in 20 fractions The absorbed dose to the spinal cord did not exceed 44 Gy In patients treated in two series 2/3 of the total target absorbed dose was given in the first series The second series was started after a rest period of 3 weeks The CRE value for treatment in one series was 1 360 and for treatment in two series 1 290 (gap correction according to WINSTON et coll 1969)

After conclusion of the irradiation s nc the patients were followed regularly in the out patient c nic As a rule no further treatment was given with the exception that some patient later received irradiation for painful bone metastases and a few patients received chemotherapy for soft tissue metastases The follow up was concluded in July 1977

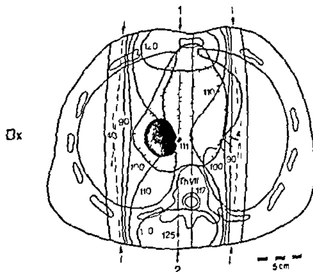


Fig 3 Distribution of the absorbed dose in a transverse section for the same patient as in Fig 2 (indicated by the dotted line in Fig 2) The tumour is indicated by black and the target volume in the section by the dotted area No correction for tissue heterogeneity ^{60}Co Size of fields 1 and 2 11 cm 18 cm SSD 70 cm 100 (Modified after ICRU Report Dose specification for reporting external beam therapy with photons and electrons 1978 By permission from ICRU Washington DC)

Results

All patients had a possible follow up time of at least 30 months The crude survival for the 2 groups of patients up to 30 months after beginning of the radiation therapy is given in Fig 4 The median survival for both groups was 8 months Three survivors in Group I have to date been followed 71 to 74 months and 5 survivors in Group II for 31 to 50 months All deaths have been scored as due to bronchogenic carcinoma although 4 patients in Group I and 3 in Group II died from causes not related to their malignant disease Of the patients receiving supplementary irradiation and chemotherapy to alleviate pain and dysfunction du to distant metastases this therapy seems to have caused a prolonged survival in only one case

Autopsies were performed on 17 patients in Group I and on 12 patients in Group II The findings are summarized in Table 5 which shows that in only 2 cases in each group was death caused by locally progressive disease with no evidence of metastases Three of these patients had well differentiated squamous cell carcinoma

Of deceased patients not examined post mortem 3 in each group had died from locally uncontrolled disease without obvious metastases Thus 5 patients in each group died exclusively of progressive intrathoracic carcinoma The majority of th patients died however from disseminated disease (e g liver brain skeleton) even though they had persistent local disease

Totally 85 patients did not receive elective irradiation of the supraclavicular fossae but in only 2 of them was this region later involved

With the fractionation and the total absorbed dose used the patients in the two groups expressed only mild complaints about their treatment As expected most patients had passing dysphagia and a dry cough at completion of the radiation therapy No spinal cord injuries occurred Radiation pneumonitis was evident in

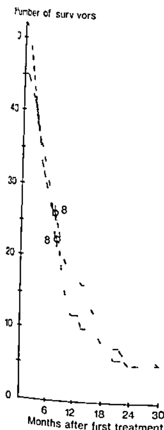


Fig 4 Number of survivors up to 30 months after the beginning of radiation therapy of patients treated in one ( ) and in two series ( ) respectively

only 3 patients However a radiography lung fibrosis was always demonstrated within the irradiated lung tissue but was of no clinical significance

Evaluation of palliative effects of irradiation on symptoms in patients with pulmonary carcinoma is often difficult since these patients usually are old and debilitated with complicating cardiovascular and respiratory diseases In the present material the effects on hemoptysis intrathoracic pain and dyspnoea were recorded in evaluable patients At the beginning of the radiation therapy 9 patients in Group I and 7 patients in Group II had significant hemoptysis which disappeared in all except one in Group II Eight and 5 patients in the two groups respectively had intrathoracic pain due to local tumour growth Of these 4 and 3 respectively were completely relieved and the remainders substantially improved Dyspnoea was more difficult to palliate only 6 of 18 patients in each group improved

Discussion

Treating pulmonary carcinoma with radiation therapy implies a difficulty in finding an adequate absorbed dose level to achieve local tumour control without causing unacceptable morbidity from organs at risk such as the heart the lungs

Table 5

Results of post mortem examination in 29 patients

	Number of patients irradiated in	
	one series	two series
No intrathoracic tumour distant metastases	1	1
Progressing intrathoracic tumour no distant metastases	2	2
Persistent intrathoracic tumour and distant metastases	14	9

and the spinal cord The present results clearly indicate that 40 Gy is a dose level insufficient for local tumour control After 30 months 8 patients in the two groups were alive without evidence of disease and therefore potentially locally cured In the patients not subjected to autopsy 2 had no indication of local tumour growth but died from dissemination of the disease This means that out of all 97 patients only 10 (10 per cent) received an absorbed dose sufficiently high for local control Opinions differ in the literature on the lowest acceptable target absorbed dose The optimum dose level for tumour control may seem to lie beyond 60 Gy if a control rate of 95 per cent is the aim (SALAZAR et coll 1976) No tumour cells were found at the primary site in 54 per cent of 24 patients treated preoperatively with 60 Gy in 6 weeks (BLOEDORN 1966) In the dose response curve for squamous cell carcinoma of the lung described by PERESLEGIN (1963) dose levels from 38 to 95 Gy were analysed yielding an optimum regression of 92 per cent at 65 Gy However if this dose level is used clinically the incidence of pneumonitis and lung fibrosis increases greatly with a decreased diffusing capacity and a reduced arterial perfusion According to BROMLEY & SZUR (1955) localized pulmonary carcinoma can be controlled in about 40 per cent of the cases with orthovoltage irradiation of moderate dose levels (47 Gy) Several authors have reported no difference in survival rates between groups of patients receiving absorbed doses of 55 to 60 Gy and those treated with smaller doses particularly between 40 and 45 Gy (SALAZAR et coll) and BELING & EINHORN (1965) found no difference in survival between patients treated with different doses between 25 and 70 Gy

The organs at risk to consider in the radiation therapy of bronchogenic carcinoma are the lungs the spinal cord and to some extent the heart and pericardium Apart from slight dysphagia related to irradiation of the oesophagus the present patients expressed no complaints clearly referrable to the treatment and *therefore* not from the organs at risk Thus no symptoms nor signs occurred from the lungs such as the evidence of acute pulmonary hypertension and pulmonary *insufficiency* from the spinal cord such as Lhermitte s sign or from the heart and *pericardium* such as abberations of cardiac rhythm or pericarditis

An absorbed dose of the order of 40 Gy over 4 weeks is probably sooner or later followed by radiation fibrosis of the lung tissue of varying degree (DEELEY 1960 HELLMAN et coll 1964) If only a part of the lung tissue has been irradiated radiation fibrosis may be absent or negligible and ventilatory functions tests indicate only little reduction usually occurring within the first year (TEATES & COOPER 1966) However irradiation of large volumes of lung tissue may often cause permanent impairment of ventilation At review of the present series it was estimated that in 25 of the 97 patients at least one third of all pulmonary tissue received the full target absorbed dose In bronchogenic carcinoma evaluation of the quality and quantity of radiation lung reactions is obscured by tumour related factors such as infection and lung function tests of patients treated with mantle technique for malignant lymphomas may be considered more representative of pure lung radiation reactions In an analysis of mantle treatment of Hodgkin s disease it was concluded that about one third to one half of all lung tissue was irradiated to an absorbed dose of about 40 Gy (SVAHN TAPPER et coll 1976) The patients had usually been irradiated in two series and the CRE value was calculated to be 1 225 or 1 100 depending on the correction method for the gap the value 1 225 being obtained when correcting according to WINSTON et coll It was concluded that for the irradiated volume and the dose time schedule used these figures eemed to represent a borderline between negligible and serious radiation lung reactions and thus may represent the tolerance limit for lung tissue in the irradiation of large volumes of pulmonary tissue The CRE values arrived at agreed well with empirically found upper limits for any major irradiation of lung parenchyma recommended by PATERSON (1963) 25 to 30 Gy in 3 weeks corresponding to a CRE value of 950 to 1 150

Radiation therapy of bronchogenic carcinoma is probably more often followed by pericardial than by myocardial reactions but usually transient ECG abnormalities are common after 22 to 23 Gy given in 3 weeks (CATTERALL 1960) An absorbed dose of 40 Gy in 4 weeks is probably only exceptionally followed by severe radiation reactions of the myocardium

The threshold dose for radiation myelopathy is usually reported to be of the order of 39 Gy in 4 weeks (BODEN 1950 PALLIS et coll 1961 PHILLIPS & BUSCHKE 1969) but lower doses have been recommended for large volumes (30 to 40 Gy in 4 weeks) The radiation sensitivity of the spinal cord seems to be time dependent and in a diagram with logarithmic scales the slope of the time dose line has been found to be 0 26 (LINDGREN 1958) or 0 21 (PALLIS et coll) Relatively higher absorbed doses may then be tolerated if the treatment is extended over a long period and provided that the absorbed dose at each fraction is not too high (ATKINS & TRETTER 1966 PHILLIPS & BUSCHKE)

The best fra tionation schedule for radia ion therapy of bronchogenic carcinoma has not yet been established Split course irradiation has the theoretical advantage of offering a good reoxygenation which hould not be counteracted by repopula ior (LEE 1974) In the present patients no difference was found between the continuous

and the split course irradiation regimens in palliative effect concerning hemoptysis thoracic pain dyspnoea local tumour control, side effects or survival at 30 months SALAZAR et coll (1976) stated that a split course regimen is superior to continuous irradiation They listed a higher percentage of tumour regression better tolerance milder radiation toxicity and a decreased incidence of local failures Split-course treatment also yielded better 12 and 18 month survival figures than the continuous therapy This agrees with previous findings reported by ABRAHAMSON & CAVANAUGH (1970) In a post mortem examination comparing 38 patients receiving split-course irradiation (60 to 70 Gy) with 29 patients given continuous treatment tumour control was more frequently found in the split course group However other investigations including randomized trials have revealed no difference in survival between groups of patients given 45 to 50 Gy in split course compared with continuous regimens (LEWITT et coll 1967) EISERT et coll (1976) found no difference in local control rate if the total absorbed dose was administered with one 2 3 or 5 fractions per week LEE (1974) reported on a randomized trial in 188 patients with unresectable bronchogenic carcinoma treated with either split course therapy (45 to 50 Gy over 7 to 9 weeks delivering half of the total absorbed dose in 12 to 14 days followed by 3 or 4 weeks of rest and then the second half of the absorbed dose in 12 to 14 days) or in one series (45 to 50 Gy over 4 to 5 weeks with 5 or 6 fractions per week) and found no difference in survival between the two groups ARISTIZABAL & CALDWELL (1976) reported on 200 patients treated with 55 to 60 Gy in 20 to 24 fractions over totally 7 or 8 weeks with an interval of 2 to 4 weeks in the middle of the period The 3 and 5 year survival rates of 19 and 16 per cent respectively for patients with well differentiated tumours confined to the lung and mediastinum alone with excellent tolerance suggested that the split course regimen had definite advantages

Thus data in the literature concerning optimum dose level and fractionation regimens are conflicting The present comparison between the effect of 40 Gy administered in a continuous manner to one group of patients and a split-course schedule administered to another group of patients has shown an obvious palliative effect on hemoptysis and thoracic pain with no difference between the groups The absorbed dose was inadequate for local control in both groups The palliative effects could be achieved without any adverse effects When irradiating bronchogenic carcinoma with 40 Gy in 20 fractions therefore irradiation in one series is now used It may be possible that better results can be accomplished with higher target absorbed dose levels but then the incidence and degree of adverse effects must be expected to rise In such case split course regimen may be advantageous Due to the tolerance limit of the spinal cord the technique may also then have to be more complicated than the simple a p —p a technique thereby often increasing the amount of irradiated lung tissue This can to some extent be counteracted by a shrinking field technique after about 40 Gy

The results of radiation therapy in unresectable bronchogenic carcinoma may be improved by a combination of irradiation and chemotherapy This was suggested

by the results of CHAN et coll (1976) in a preliminary investigation combining Bleomycin and conventional irradiation Whether substances with experimentally documented radiation sensitizing properties are of value in this respect remains to be demonstrated

SUMMARY

Patients with unresectable or inoperable bronchial carcinoma were treated with en bloc irradiation of the tumour and the mediastinal lymph nodes to a total target absorbed dose of 40 Gy in 20 fractions The first 52 patients were treated in one series and the last 45 patients in two series (split course) Radiation adverse effects were only mild The two regimens gave the same palliative results The median survival was the same for the 2 groups (8 months) Most patients died in disseminated disease

ZUSAMMENFASSUNG

Patienten mit nicht resezierbaren oder inoperablem Bronchial Karzinom wurden mit einer en bloc Bestrahlung des Tumors und der mediastinalen Lymphknoten mit einer absorbierten Gesamt Dosis im Target Bereich von 40 Gy in 20 Fraktionen behandelt Die ersten 52 Patienten wurden in einer Serie und die letzten 45 Patienten in zwei Serien (split course) behandelt Die nachteiligen Strahleneffekte waren gering Die beiden Methoden gaben dieselben palliativen Resultate Die mittlere Überlebenszeit war dieselbe fur beide Gruppen (8 Monate) Die meisten der Patienten starben an einer disseminierten Erkrankung

RÉSUME

Des malades atteints de carcinome bronchique inextirpables ou inopérables ont été traites par une irradiation en bloc de la tumeur et des ganglions lymphatiques médiastinaux avec une dose absorbee totale à la cible de 40 Gy en 20 fractions Les 52 premiers malades ont éte traités en une serie et les 45 derniers en deux series (split-course) Les effets nocifs des rayons ont ete legers ces deux traitements ont donné les memes résultats palliatifs La survie médiane a été la meme pour les deux groupes (8 mois) La plupart des malades sont morts avec une dissemination de leur affection

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POSTOPERATIVE IRRADIATION OF GLIOBLASTOMAS

Results in a randomized series

A P ANDERSEN

Glioblastoma multiforme is the most common form of tumour in the cerebral hemispheres and represents about 40 per cent of the total number of cerebral gliomas

Differences of opinion exist regarding the efficacy of irradiation Many authors at least in the past thought irradiation useless while others were of the opinion that the treatment of choice was primary surgical decompression and removal of malignant tissue followed by adequate irradiation (LINDGREN 1969)

In the series of BOUCHARD (1966) treated with a combination of operation and irradiation 44 per cent survived one year This result was compared with a series of FRAENKEL & GERMAN (1958) treated by surgery alone in which only 7 per cent survived one year Drawing upon these results BOUCHARD recommended postoperative irradiation Also TAVERAS et coll (1962) found a prolonged survival in a series of glioblastomas when the operation was combined with postoperative irradiation

SHELINE (1977) has collected data concerning the effect of postoperative irradiation in glioblastoma multiforme (malignant glioma grade IV) from four American clinics Mayo Clinic (UIHLEIN et coll 1966) University of California Los Angeles (STAGE & STEIN 1974) Jefferson University (KRAMER 1973) and University of California San Francisco (SHELINE 1975)

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Table 1

Distribution according to year of treatment during trial period 1 1 1963–30-4 1967

Year	No of cases
1963	30
1964	20
1965	25
1966	22
1967	11
Total	108

The survival rates at one year were 24 per cent in irradiated series compared with 8 per cent in non irradiated At three years 6 per cent of the irradiated patients were living but all of the non irradiated were dead

All these reports are impaired by absence of randomization In the literature no randomized series from the same clinic and in the same period has been found to evaluate the effect of postoperative irradiation in glioblastomas

Therefore in these departments a randomized investigation was performed between the 1st of January 1963 and the 30th of April 1967 The randomization was carried out as follows Patients who were born on even dates should only be operated upon while patients born on uneven dates should in addition receive postoperative irradiation

The irradiation wa given as soon a possible after the operation that is when the wound had healed and the general condition of the patient permitted it In most cases the irradiation began less than two weeks after the operation and was given with a cobalt unit Two parallel opposing fields were used one on each side of the head and in most cases the entire intracranial content was irradiated In single cases in which the tumour seemed to be more localised only the tumour area and a reasonable surrounding area was irradiated A tumour dose of 45 Gy in 4½ to 5 weeks was administered with 5 or 6 fractions a week A higher dose was never used to assure certain avoidance of cerebral necrosis This treatment regimen was generally well tolerated

Material

The material consisted of 108 patients The distribution according to the year of treatment appears in Table 1 and the age and sex distribution in Fig 1 The malignant glioma grade 4 is most common in the 6th and 7th decade of life and is twice as frequent in males as in females

All histologic specimens were evaluated by the same neuropathologist Gliomas

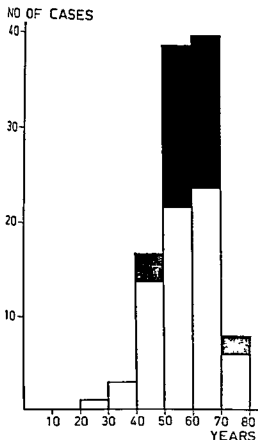


Fig. 1 Distribution by age (years) and sex ■ Females (9 cases) □ Males (69 cases)

of lower grade than grade 4 are not included in the material nor in cases in which a primary biopsy had shown astrocytoma while a later biopsy in connection with recurrence and re-operation had shown glioblastoma All cases were controlled at regular intervals and the follow up was complete All survival curves are calculated as crude survival and the date of operation is used as the beginning of the observation period

Results

Total material The survival curve for the total material (Fig 2) indicates that the primary mortality is considerable i e 25 per cent of the patients died within one month and only 6 per cent survived one year The separate survival curves for males and females (Fig 3) show that no difference between the sexes exists A comparison between patients older and younger than 60 years appears in Fig 4 The most important difference between the two groups is found in the primary mortality

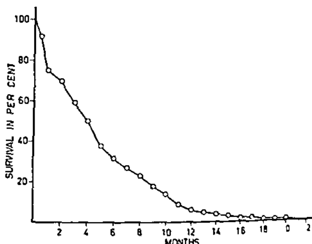


Fig 2 Crude survival of total material (108 cases)

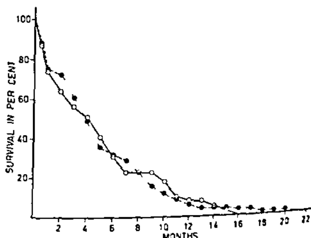


Fig 3 Crude survival according to sex ○ females (39) ● males (69)

within the first two months After that time the curves are nearly parallel with a tendency to converge against one year

The group of glioblastomas indicates several subgroups with differing microscopic appearance The number of cases in the present material does not permit a comparative evaluation of these subgroups The differentiation of these subgroups is also a matter of dispute but it is generally accepted that the angionecrotic type is the most malignant and has the poorest prognosis Therefore a comparative evaluation was made between this and the other types (Fig 5) This comparison confirmed the opinion that the angionecrotic type is the most serious a closer analysis revealed however that the greatest difference is found in the primary mortality and that the difference in number of long term survivors is less marked

Value of postoperative irradiation The survival curves for the two randomized groups are given in Fig 6 Patients born on even dates should belong to the irradiated

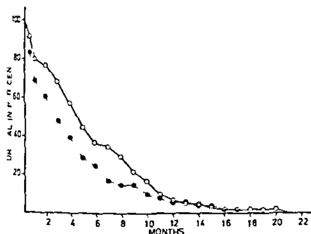


Fig 4 Crude survival according to age groups ● over (60 cases) ○ under 60 years (48 cases)

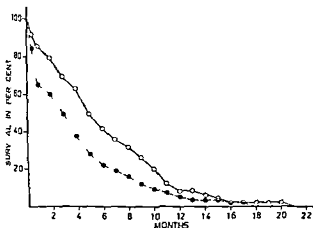


Fig 5 Crude survival according to type of tumours ● angionecrotic (58 cases) ○ other types of glioblastoma (50 cases)

group but nevertheless 11 patients did not receive any irradiation This was due either to a general condition too poor for irradiation or to the fact that death occurred in connection with the operation The two curves follow each other during the first two months after the operation but then diverge Six months after the operation the difference between the two groups is significant at the 5 per cent level ($p < 0.05$)

A better evaluation of the value of the irradiation is obtained if all cases which have not survived 2 months are excluded (Fig 7)

The irradiated group then consisted of 36 cases (28 males 8 females) and the non irradiated group of 39 (22 males 17 females) However in the irradiated group only 30 were given the intended dose because 4 patients were in too poor a general condition and in 2 cases the patients families wished the treatment to be discontinued

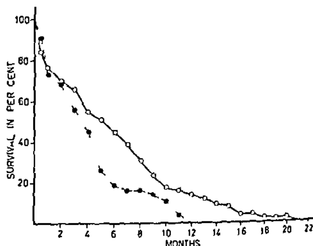


Fig 6 Crude survival according to irradiated (○ 51 cases) non irradiated (● 57 cases)

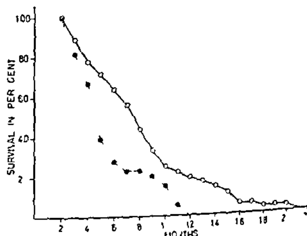


Fig 7 Crude survival of the irradiated group (○ 36 cases) compared with the non irradiated group (● 39 cases) Patients who survived less than 2 months after operation excluded

From Fig 7 it is evident that the irradiation improved the prognosis Th difference between the two groups 6 months aft r the operation is significant at th 0 5 per cent level (p 0 005) Furthermore only patients from the irradiated gro survived one year (7 patients)

The two groups were compared with regard to age and microscopic type (Table 2 3) The distribution is equal in these respects but there were more females in th non irradiated group However no difference in the general prognosis was foun between males and females (Fig 3) and therefore this fact can scarcely be of im portance for the difference between the two groups

Discussion

The results seem to indicate that postoperative irradiation improves the prognosis which however is still very poor

Table 2

Irradiated and non-irradiated groups divided according to age (patients not surviving 2 months excluded)

Age	20–29	30–39	40–49	50–59	60–69	70–79	Total
Irradiated group	0	2	7	1_	13	2	36
Non irradiated group	1	1	7	16	12	2	39

Table 3

Irradiated and non-irradiated groups divid d accord ng to microscopic type (patients not surviving 2 months excluded)

Microscopic type	Angionecrotic	Others	Total
Irradiated group	16	20	36
Non irradiated group	19	20	39

Some factors which may influence the evaluation of the value of the irradiation must be considered The system of randomizing used made it possible for the neurosurgeon in advance to know to which group the patient belonged In principle this is not correct but it seems to be irrelevant for the conclusions drawn

Another factor which could be of importance is that patients in the irradiated group had been under medical care 4 to 6 weeks longer than the non irradiated group However the majority of patients in the non irradiated group were sent for medical care in local hospitals especially if the patient s general condition was unsatisfactory

A repeat operation because of recurrence was performed in 7 of the 108 patients 6 being in the 4th and 5th decade of life Of the re operated patients 6 belonged to the irradiated group and one to the non irradiated On average these patients survived 7½ weeks after the re operation and it is doubtful whether this operation prolonged the survival time

No accurate evaluation of the grade of recovery was made but no essential difference seems to exist between the two groups

The present results are not so encouraging as those reported by others Bouchard (1966) reported a 1 and 3 year survival of 44 and 13 per cent respectively Lindgren (1965) 42 and 12 per cent respectively Stenberg & Moberg (1971) found in their series 4 of 13 surviving one year but none two years and Onoyama et coll (1976) found in a series of 127 cases 52 per cent surviving one year 19 per cent 3 and 12 per cent 5 years In all these series operation was combined with irradiation

The explanation of these considerable differences in treatment results is probably to be found in differences in the microscopic classification Some classify these lesions to microscopic type and others to the degree of malignancy The term glioblastoma multiforme has without doubt in many cas s been used as a general term

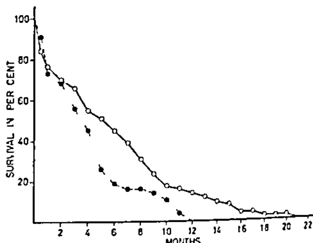


Fig 6 Crude survival according to irradiated (○ 51 cases) non irradiated (● 57 cases)

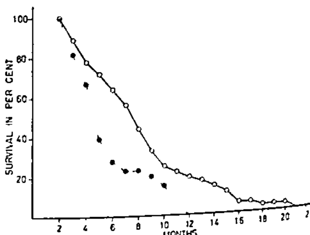


Fig 7 Crude survival of the irradiated group (36 cases) compared with the non irradiated group (● 39 cases) Patients who survived less than 2 months after operation excluded

From Fig 7 it is evident that the irradiation improv d the prognosis The difference between the two groups 6 months aft r the operation is significant at the 0 5 per cent level (p 0 005) Furthermore only patients from the irradiated group urvived one year (7 patients)

The two groups were compared with regard to age and microscopic type (Tables 2 3) The distribution is equal in these respects but there were more females in the non irradiated group However no difference in the general prognosis was found between males and females (Fig 3) and therefore this fact can scarcely be of importance for the difference between the two groups

Discussion

The results seem to indicate that postoperative irradiation improves the prognosis which however is still very poor

the postoperative irradiation The irradiated cases had a 6-month survival rate of 64 per cent and a one year survival rate of 19 per cent the non irradiated cases a 6-month survival rate of 28 per cent and a one year survival rate of 0 per cent

ZUSAMMENFASSUNG

Ein Material von 108 Patienten mit Glioblastoma wird beschrieben Die Serie wurde in zwei Gruppen eingeteilt Patienten die nur operiert wurden und Patienten die zusätzlich postoperative Bestrahlung erhielten Die Patienten die innerhalb von 2 Monaten nach der Operation gestorben waren wurden ausgeschlossen um den wirklichen Wert der postoperativen Bestrahlung festzustellen Die bestrahlten Patienten hatten eine 6-Monate Überlebensrate von 64 Prozent und eine ein Jahr Überlebensrate von 19 Prozent Die nicht bestrahlten Patienten hatten eine 6-Monate Überlebensrate von 28 Prozent und eine ein Jahr Überlebensrate von 0 Prozent

RESUMÉ

L auteur presente une série de 108 malades atteints de glioblastome Cette serie a été repartie de façon aleatoire en deux groupes les cas qui ont éte seulement operés et ceux qui ont subi en plus une irradiation post opératoire Les malades decédes dans les deux mois après l operation ont été exclus pour estimer l interet reel de l irradiation post operatoire Les cas irradies ont eu un taux de survie a 6 mois de 64 pour-cent et un taux de survie a 1 an de 19 pour cent Les cas non irradiés ont eu un taux de survie à 6 mois de 28 pour-cent et un taux de survie a 1 an de 0 pour-cent

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MUCOSAL PROTECTION DURING IRRADIATION OF EXTERIORIZED RAT ILEUM

Effect of hypoxia induced by starch microspheres

J O FORSBERG B JUNG and B LARSSON

The concentration of dissolved molecular oxygen generally influences radiation injury in all biologic systems

Degradable microspheres were recently introduced as a means for obtaining local hypoxia (ARFORS et coll 1976) blocking the circulation at the arteriolar level for several minutes

Hypoxic radiation protection of the hind foot of the rat and evaluation of injury to the skin yielded a dose modification factor of 0 50 (FORSBERG et coll 1978) In similar experiments the effects of transient intestinal hypoxia on body weight and bowel function of rats were evaluated after a single dose of roentgen rays to the whole abdomen (FORSBERG & JUNG 1978) A protective effect was observed but the dose modification factor could only be estimated with some reservations

Therefore an experimental system has been designed to allow a more elaborate analysis of the protective effect of degradable microspheres on the exteriorized rat gut The model for protected animals included a selective injection of spheres into the superior mesenteric artery Irradiation was given as a single dose of roentgen rays Mucosal weight and microscopic appearance of the intestinal wall 4 days after irradiation were evaluated

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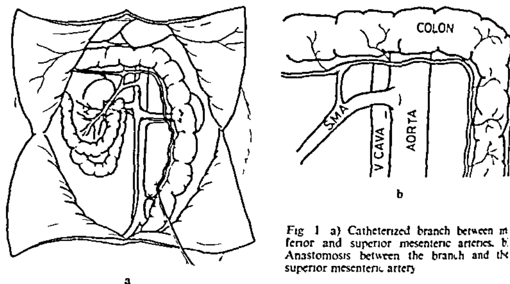


Fig 1 a) Catheterized branch between in ferior and superior mesenteric arteries. b) Anastomosis between the branch and the superior mesenteric artery

Material

Sprague Dawley male rats weighing about 300 g fed on a standardized diet and with free access to food and water were used After the experiments the animals were kept in separate cages The material was divided into one protected and one non protected group which were subjected to identical surgical procedures but for arterial catheterization and were then given graded doses of radiation (Table) Two non irradiated control groups one sham operated and one non operated were used for comparison of the mucosal weights

The degradable microspheres were cross linked starch molecules (Pharmacia) with a diameter of 44 ± 7 μm suspended in physiologic saline (80 mg/ml 6 8 10⁶ spheres ml) The degrading half times of 6 75 × 10⁶ spheres were 20 and 10 min in 20 ml of buffered saline with 240 and 1 500 IU standard amylase respectively (N GREN 1976)

The animals were anaesthetized by intraperitoneal mebumal sodium (ACO 40 mg kg) administered 30 min before irradiation Via a midline abdominal incision

Table

Irradiation doses and number of irradiated segments for each dose in the non-protected groups and in the protected groups

Non protected										
Gy	5 5	7 0	8 5	10 0	11 5	13 0	14 5			
No	6	15	8	15	9	15	6			
Protected										
Gy	10 5	12.8	15 0	17 3	19 5	20 0	[illegible]3 0	16 0	30 0	34 0
No	8	9	9	7	9	7	7	6	5	7



Fig 2 Exteriorized ileal segment in irradiation box

the inferior mesenteric artery was identified and ligated close to the aorta After incision in a branch anastomosing with the superior mesenteric artery a thin catheter filled with heparinized saline was introduced in the direction of the superior mesenteric artery and fixed with ligatures (Fig 1)

The small gut was then exteriorized Starting at a point 10 cm from the ileocecal valve and proceeding in the proximal direction the distal part of the ileum was marked into five segments each 4 cm long with 5 cm long interspaces The markings were made with 6 0 silk ligatures which were loosely knit in loops around a terminal arcade artery close to the gut wall so as not to interfere with the circulation The gut was then placed back into the abdomen In the non protected group arterial catheterization was not performed With the animal on side the segment of the gut to be irradiated was exteriorized into a plastic box 8 cm × 8 cm × 3 cm filled with saline kept at 37 C by a thermostat (Fig 2) The segments were easily identified by the silk loops A plastic net 5 mm below the saline surface kept the segment in a horizontal position The radiation field was 5 5 cm × 5 5 cm and the beam was directed vertically from beneath One border of the irradiation field was placed close to the edge of the box and tangentially to the animal s abdomen which was screened by an extra 3 mm lead to reduce the abdominal dose due to scattered radiation A 3 mm plate of plastic together with 15 mm of saline secured an adequate dose build up

In the protected animals 0 4 ml of the microsphere suspension was then injected into the catheter The induced ischemia was confirmed by inspection (FORSBERG 1978) Exactly 5 min after the injection the irradiation was started the most distal segment always being irradiated first The radiation doses to the consecutive segments were chosen at random a set of five pres lected combinations in order to reduce the influence from possible differences in the radiation response along the gut

After irradiation the segment was placed back into the abdomen and the next segment proximal to the one just irradiated was exteriorized The same procedure was repeated for the remaining segments In most cases there was sufficient time for irradiation of the five segments under deep hypoxia In a few animals recirculation came too fast and some segments had therefore to be excluded from the serie



Fig 3

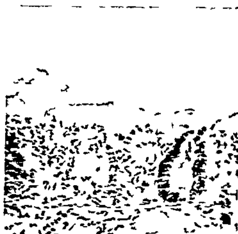


Fig 4

Fig 3 Ileal segment irradiated with 7 Gy with slightly affected mucosa Villi decreased in height but the epithelium appears normal 160

Fig 4 Non protected segment irradiated with 10 Gy Only a few crypt like formations remain in the mucosa villi destroyed but remnants appear as ghost villi 160



Fig. 5



Fig 6

Fig 5 Non protected segment irradiated with 10 Gy The normal structure is deranged wide capillaries appear in the central cord of the deformed villi The columnar epithelium of the villi is replaced by atypical cells Inflammatory cells in the stroma 160

Fig. 6 Non protected segment after 10 Gy Maximum destruction of epithelial structures No epithelial cells in any layer of the mucosa Marked inflammatory reaction and wide capillaries 160

After the experiment the arterial branch was ligated and the catheter removed The abdomen was closed after deposition of 5 ml of saline

Irradiation was performed with 8 MV roentgen rays from a linear accelerator (MEL SL Super 600 pulses s pulse length 2 μs source to-skin distance 73 cm

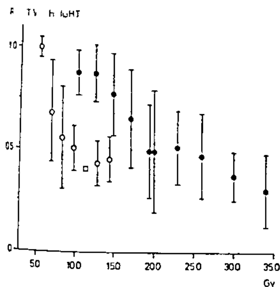


Fig 7 Mucosal height of non protected segments (○) and protected segments (●) relative to height of continuous non irradiated segment Mean and SD

mean dose rate 13 Gy/min) The radiation dose was measured with radiation sensitive diodes (Scanditronix DPD 5 Uppsala Sweden) The scatter dose to the centre of the animal was 2 5 per cent of each segment dose given For the non protected animals the scattered doses were 1 25 to 1 34 Gy and for the protected 1 87 to 3 33 Gy The uncertainty in the relative nominal doses in the gut was estimated to be within ±1 per cent

The irradiation procedure was the same for both the non protected and the protected animals

Microscopy and mucosal water content The animals were killed after 4 days The gut was removed and the segments were identified All segments were handled in the same way and by the same investigator without knowledge of the segmental doses The irradiated segment was cut out together with a contiguous non irradiated segment and was opened lengthwise Luminal contents if present were gently removed From 1 cm length of the relaxed irradiated segment the mucosa was removed from the muscle layer with a sharp dissection knife and measured for wet and dry weight The specimens taken for microscopy were fixed in 6 per cent formaldehyde and stained with Htx eosin

In the microscopic evaluation of the radiation effects the following three variables were considered (1) gross changes in the epithelial structure (2) estimated number of villi per mm gut and (3) the height of the mucosa The height from the sub mucosal layer to the gut lumen was measured and the relation between the mucosal height of the irradiated segment and the contiguous non irradiated segment was calculated

The mucosal weight and the water content from the irradiated and control segments was determined by a freeze drying technique (−80 C 24 h)



Fig 8 Protected segment after 20 Gy Villi height normal and epithelial cells columnar Wide capillaries in top of villi indicate injury ×160

Statistics The doses for effect in 50 per cent of the protected and non protected groups were determined by probit analysis (BEYER 1968) The two variables in the error function were determined by weighted least squares techniques and their uncertainties by matrix inversion

Results

Of the 31 rats none died before schedule Some of the animals developed moderate irradiation sickness anorexia and diarrhea On the fourth day when the rats were killed the gut on inspection had a quite normal macroscopic appearance apart from reddening of the irradiated segments

The animals were irradiated at 6 different occasions No systematic differences were found in the results from the animals irradiated on different occasions

Microscopy As every specimen of an irradiated segment also contained a part of a non irradiated segment a direct comparison with the unaffected mucosa could be made

At the lower dose levels the most obvious response to irradiation in the non protected segments was a decrease in the number and height of the villi the epithelium appearing almost normal when compared to the adjacent non irradiated



Fig 9



Fig 10

Fig 9 Protected segment after 20 Gy Villi height almost normal and villi still well recognizable but lined by atypical cells with nucleus often located centrally 160

Fig. 10 Protected segment irradiated with 23 Gy Normal structure of villi and crypts can still be detected but epithelial cells abnormal villi broad and abundant inflammation Abnormal cells on top of the villi often in the form of clusters 160

mucosa (Fig 3) With more severe epithelial injury the muscular wall was thickened presumably due to oedema the number and height of villi had further decreased and the villi had widened Wide capillaries were demonstrated most easily in the villi tips The columnar epithelial lining of the tips vanished leaving ghost villi (Fig 4 SEBES et coll 1975) and the regular appearance of crypts and villi was broken up In many specimens few but low broad villus formations were found with a very thin epithelial lining of cells of atypical appearance presumably similar to the ω cells described by PATT & QUASTLER (1963 Fig 5) At the next higher level of injury only few islets of epithelial cells remained deep in the destroyed mucosa (Fig 4) At the highest level of injury all epithelial cells had disappeared (Fig 6) In the more heavily damaged specimens a varying amount of inflammatory cells was present After 7 Gy villi still remained although reduced in number in 55 per cent of segments and after 8 5 Gy in 22 per cent The height of the mucosa relative to the non irradiated contiguous segments is given in Fig 7

In the protected segments similar reactions were demonstrated as in the non

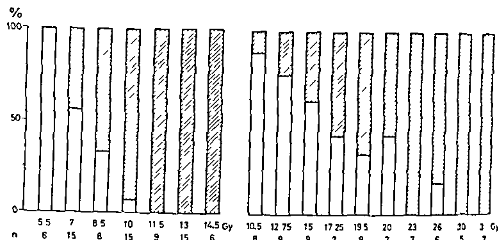


Fig 11 Microscopic evaluation of irradiation effect on mucosal epithelium in non protected (left) and protected (right) segments Each bar represents 100 of the segments irradiated with the same dose n = No of segments evaluated Striped = distinct epithelial injury

protected but only at considerably higher doses Here before a change in the epithelial lining and in cell shape was evident wide capillaries indicated injury (Fig 8) At the most severe levels of injury atypical cells occurred (Fig 9) and the regular appearance of villi and crypts disappeared (Fig 10) In the protected segments villi could still easily be distinguished and counted in 43 per cent of segments irradiated with 20 Gy The relative height of the mucosa is given in Fig 7

The epithelial injury could be classified with confidence in the two groups one almost normal and the other with distinct signs of injury To the first group belonged the segments with an epithelial appearance that did not differ appreciably from the contiguous non irradiated segment In some of these segments the villi were lower than in the contiguous non irradiated ones but no major change in the crypts or villus number was seen (Fig 3) The other group included the rest of the segments having major epithelial injury indicated by atypical cells or loss of cells The villi were generally few low or deleted The crypt epithelium could be fairly abundant but was most often represented by sparsely scattered islets The two groups are presented in Fig 11

The probit analysis shows that the dose modification factor defined as the quotient between the doses for a 50 per cent incidence of major injury in the non protected and protected segments respectively was 7 55/17 26 $0\,44 \pm 0\,04$ (95 confidence limit) corresponding to an oxygen enhancement ratio of $2\,3 \pm 0\,3$ The dose effect curves are plotted in Fig 12

Weight of mucosa and its water content The precision in the mucosa sampling was roughly estimated to be _ 10 per cent The wet and dry weights of the mucosa specimens are given in Fig 13 Significantly more tissue is saved in the protected segments An estimate at two different weight levels (control and 60 per cent of control) gave a dose modification factor of $0\,42 \pm 0\,05$ and $0\,44 \pm 0\,06$ respectively

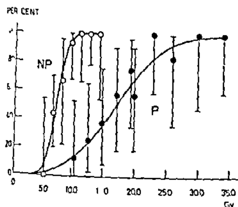
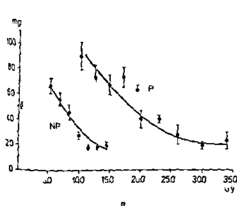


Fig 12 Incidence (per cent) of major epithelial injury in protected (P) and non protected (NP) segments versus absorbed dose (Gy) Error bars represent 95 confidence limit Curve obtained from probit analysis Underlying data the same as in Fig 11



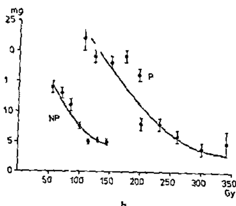


Fig 13 Weight of mucosa of 1 cm gut in non protected (NP) and protected (P) segments as function of dose O indicates control segments Mean and SEM a) Wet weight b) dry weight

The water content of the mucosa calculated per g dry tissue and related to the corresponding water content of the control segments did not differ significantly independent of irradiation

Discussion

The evaluation of radiation injury was performed about 96 h after the irradiation trauma At this time the injury of the mucosa from the higher doses should be close to its maximum (MAISIN et coll 1971) whereas the segments irradiated with lower doses should be partially recovered

The microscopic findings in the non protected segments were in good agreement with the reaction generally reported after irradiation (QUASTLER 1963 MAISIN et coll) For the protected segments likewise an agreement existed with some reports of mucosal protection by clamping of the superior mesenteric artery (PRASAD et coll 1963 SEBES et coll PENN et coll 1975) An obvious difference in the cellular response to irradiation was also found between the non protected and the protected groups

In the non protected segments atypical cells appeared first when the villi were considerably reduced in height but in the protected segments they were sometimes evident in villi of almost normal height The epithelium of all the protected segments had a normal microscopic appearance at 10 5 Gy a situation encountered in the non protected group only at 5 5 Gy

From the probit analysis the doses for 50 per cent incidence of major injury in the two groups were found to be 7 55 Gy and 17 26 Gy respectively The 95 per cent confidence ranges for the two estimates were $\pm 0\ 36$ Gy and $\pm 1\ 09$ Gy respectively The dose modification factor for this injury level is then calculated as $0\ 44 \pm 0\ 04$ corresponding to an oxygen enhancement ratio of $2\ 3 \pm 0\ 3$

The microscopic evaluation was based on distinct differences Only easily recognized changes in the villus number height and shape as well as gross changes in the mucosal epithelium were taken into account A possible influence du to differences in villus height and number along the gut was reduced as the comparison was made between irradiated villi and contiguous non irradiated villi only The response of different segments to a certain dose was not always the same (Figs 3-10) This variation may be explained by inter individual difference in radiation sensitivity

The higher relative weights of the mucosa samples from the non protected segments in the lower dose range when compared to the non irradiated segments (Fig 13) may be explained by a possible overcompensation in cell activity with hypertrophy of the villi This phenomenon has been observed on the third day after irradiation by WILLIAMS et coll (1958) and WIERNIK (1966)

A similar effect may also explain the considerably higher relative weights of the specimens for the protected segments up to a dose of about 20 Gy (Fig 13)

The mucosa sampling for weight measurements is not an exact method but the results roughly indicate preserved mucosal mass The agreement with the dose modification factor determined from the microscopic grading is rewarding The sampling method was used by KAY & ENTENMAN (1959) and their dose response curves are quite similar to the present ones

Evaluation of the water content of the mucosa did not indicate diminished oedema in the protected mucosa A tendency existed towards a lower water content at the higher doses in protected and lower doses in non protected animals but the difference from the control values was not significant

In a previous work protection against the abdominal radiation reaction by degradable microspheres injected into the aorta was reported (FORSBERG & JUNG) The dose modification achieved was significant but less apparent than that in the present series The difference might be explained by the fact that in the previous experiments the whole abdomen was irradiated The ileum was probably adequately protected but other organs in the radiation volume—duodenum spleen liver and bone marrow of the spine—were probably only partially protected

The fairly low dose modification factor found in the present series strongly supports the concept that degradable microspheres can be used to protect selected organs

at risk in radiation therapy To this end work is in progress to evaluate the use of spheres in fractionated irradiation

Acknowledgements

This investigation was supported by the Swedish Cancer Society The irradiations were performed at the Department of Oncology Akademiska Sjukhuset Uppsala

SUMMARY

Transient hypoxia induced by intra arterial injection of degradable starch microspheres was used for protection of exteriorized segments of the rat ileum Microscopic evaluation of the injury to the mucosa gave a dose modification factor of 0 44 ± 0 04 which corresponds to an oxygen enhancement ratio of 2 30 A similar factor was also found from measurements of the mucosal weight No significant development of mucosal oedema could be demonstrated neither in protected nor in non protected segments

ZUSAMMENFASSUNG

Eine verubergehende Hypoxie wurde durch intraarterielle Injektion von abbaubaren Starke Mikrospharen hervorgerufen und verwendet um herausgelegte Segmente des Ileums der Ratte zu schutzen Die mikroskopische Auswertung der Schadigung der Mukosa ergab einen Dosis Modifikationsfaktor von 0 44 ± 0 04 welcher einem Sauerstoff Steigerungsgrad von 2 30 entspricht Ein ahnlicher Faktor wurde auch bei Messungen des Gewichts der Mukosa gefunden Es konnte keine signifikante Entwicklung eines Mukosaodems nachgewiesen werden weder in geschutzten noch in ungeschutzten Segmenten

RESUME

Les auteurs ont utilise une hypoxie transitoire provoquée par l injection intraarterielle de microsphéres d amidon degradable pour proteger contre l irradiation des segments exteriorises d ileon du rat L évaluation microscopique des lésions de la muqueuse a donne un facteur de modification de doses de 0 44 ± 0 04 qui correspond a un rapport de renforcement par l oxygène de 2 30 Les mesures du poids de la muqueuse ont donné aussi un facteur semblable Les auteurs n ont pas pu mettre en évidence d apparition significative d œdeme de la muqueuse ni dans les segments protégés ni dansl es segments non proteges

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DEMOGRAPHIC INVESTIGATION OF MAMMARY CARCINOMA IN NORTHERN SWEDEN

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It is well known that most types of malignant tumours have a very unequal global distribution (cf MUIR & PERON 1976) This is regarded mainly as an expression of the influence of environmental factors although genetic factors also play a role Differences between the incidences of malignant tumours in different continents or in countries may be very great and significant inequalities between geographic areas within a country have also been demonstrated Good examples of the latter mentioned type of variation are to be found in the atlas of cancer mortality for the white population in U S counties 1950–1969 (MASON et coll 1975) and in the 7 year report concerning the incidence of malignant tumours in Sweden 1959–1965 (Swedish Cancer Registry 1971)

The three northernmost counties in Sweden constitute a geographic area which from several points of view is of interest for demographic investigation of malignant diseases It is a vast area which contains several relatively well separated regions such as towns with heavy industry towns with very little industry and large rural areas A limitation for epidemiologic investigations in this region is the rather small population of approximately 750 000 By use of the cumulated incidence during an available 13 year period (1959–1971) from the Swedish Cancer Registry it is however expected that significant information will be obtained regarding the more frequent types of malignant tumours

Submitted for publication 16 February 1978

Table 1

Comparison between incidence rates of female breast carcinoma (standardized with reference to European standard population)

	Incidence rate (per 100 000 per year)
Europe	
Denmark	68
Iceland	68
Sweden	73
United Kingdom (6 regions)	67 74
West Germany (2 regions)	66 69
Switzerland (Geneva)	97
Norway	61
Finland	45
East Germany	45
Hungary (2 regions)	26–39
Poland (5 regions)	20–43
Romania (Timis)	39
Yugoslavia (Slovenia)	38
Asia	
Japan (3 regions)	16–22
Israel Jews	74
Israel non Jews	15
India (Bombay)	28
New Zealand whites	71
North America	
California whites (2 regions)	103 109
California blacks (2 regions)	76–78
Connecticut	98
Iowa	85
New York State	79
Canada (7 regions)	59 109
Africa	
Nigeria (Ibadan)	0
Rhodesia Africans (Bulawayo)	18

The findings concerning female breast carcinoma are stated in the present report Quite remarkable geographic differences in incidence have previously been reported for this type of carcinoma In Table 1 age standardized incidence rates for some European American Asian and African areas are listed according to reports in Cancer Incidence in Five Continent Vol III (IARC 1976) The incidence rate is generally high in western Europe USA Canada New Zealand and among the Jewish population in Israel considerably lower in most countries in eastern Europe and remarkably low in Japan and in Africa The breast carcinoma mortality in the pr

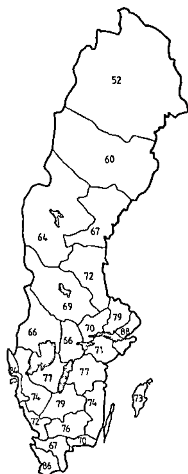


Fig 1 Age standardized incidence rates for female breast carcinoma in Swedish counties 1959–1971 (per 100 000 and year)

viously mentioned investigation of the mortality in malignant diseases in U S counties (MASON et coll) was generally higher in the northern urban areas particularly in the Northeast than in the South In Sweden the highest incidence rates are to be found in some counties in the central and southern parts of the country Counties in northern Sweden have in general lower incidence rates (Fig 1)

Interesting differences have also been reported as regards the age specific incidence rate of breast carcinoma In high incidence regions the rate increases continuously with age with the exception of the menopausal decade during which the curve temporarily flattens out (Clemmesen s hook) In low incidence regions the curve is bimodal with a peak in the premenopausal age (DE WAARD et coll 1960 DE WAARD 1969 HAKAMA 1969) The great difference between low incidence and high incidence regions concerns the frequency of postmenopausal carcinoma In Iceland it has been possible to follow the age specific incidence rate during the past six decades and to

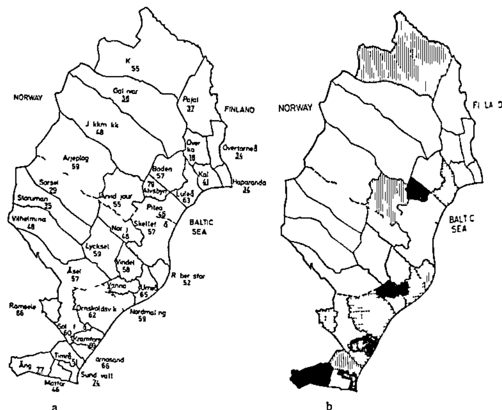


Fig 2 Age standardized incidence rates for female breast carcinoma in the municipalities of northern Sweden 1959–1971 a) Numerical rates for each municipality (underlined figures are significantly different from the rate for the whole area $p < 0.05$) b) Age standardized incidence rates for the municipalities expressed as per cent of the corresponding rate for the entire area ▪ = 115 ▢ = 105–114 ▢ = 95–104 ▥ = 85–94 ▢ = –84

observe how it has gradually changed from low incidence type to high incidence type (BJARNASON et coll 1974)

Several etiologic factors based partly upon epidemiologic observations have been discussed regarding female breast carcinoma (cf LEIS 1976) Breast carcinoma in a woman s family history seems to double such a woman s risk for developing this type of malignancy (ANDERSEN 1976) Low parity and late age at first delivery are also factors which seem to be correlated to the incidence of breast carcinoma (MAC MAHON et coll 1973 WYNDER et coll 1960 a o) However in a recent report from Sweden no influence from the reproductive history on the breast carcinoma risk could be demonstrated (ADAMI et coll 1977) A much discussed factor is the dietary fat intake and on a country level a close correlation has been demonstrated between fat intake and the incidence of breast carcinoma (CARROLL et coll 1968 ARMSTRONG & DOLL 1975) The demonstrated correlations between the incidence of mammary and colo-rectal carcinoma may support the theory of an etiologic dietary factor (WYNDER et coll 1969 DRASAR & IRVING 1973 JANSSON et coll 1975) Breast car

Table 2

Mean female population number of cases and age standardized incidence rates for breast carcinoma 1959 to 1971 in counties provinces and municipalities in northern Sweden

	Mean female population	Number of new breast carcinoma cases	Age standardized rate
Vasternorrland County	134 201	1 172	67 ± 3
Medelpad	59 239	517	67 ± 5
Ånge	8 238	90	77 ± 15
Matfors	4 9_1	34	46 + 15
Sundsvall	35 658	3 0	74 ± 7
Timrå	10 4?2	73	51 ± 11
Ångermanland	74 96?	655	64 ± 5
Harnosand	14 133	1_4	66 ± 11
Kramfors	15 7_2	173	69 ± 10
Örnsköldsvik	29 917	228	62 ± 7
Sollefteå	12 941	108	60 ± 11
Ramsele	2 249	22	66 ± 25
Vasterbotten County	114 474	765	60 ± 4
Vasterbotten	88 130	673	61 ± 4
Nordmaling	4 305	35	59 ± 18
Vindeln	4 227	32	58 ± 19
Robertsfors	4 047	31	52 ± 17
Norsjo	5 _90	28	46 ± 15
Vannas	5 991	52	74 ± 18
Umeå	30 611	_03	65 ± 8
Skellefteå	35 609	248	57 ± 7
S Lappland	26 344	142	48 ± 7
Storuman	4 591	17	35 ± 16
Sorsele	2 406	9	29 ± 18
Vilhelmina	4 512	25	48 ± 17
Åsele	5 125	37	57 ± 17
Lycksele	7 460	48	59 ± 16
Norrbotten County	1 5 869	653	52 ± 4
Norrbotten	86 045	478	51 ± 4
Piteå	15 330	8?	46 ± 10
Älvsbyn	4 521	38	79 ± 22
Luleå	25 944	162	63 ± 9
Boden	13 976	91	57 ± 10
Kalix	8 936	45	41 ± 12
Överkalix	3 602	7	18 ± 13
Haparanda	4 768	19	34 ± 15
Övertorneå	4 167	14	34 ± 16
Pajala	6 0_7	22	? ± 15

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Table 2 (*cont*)

	Mean female population	Number of new breast carcinoma cases	Age standardized rate
N Lappland	39 824	175	47±7
Arvidsjaur	4 490	29	55±19
Arjeplog	2 368	16	59±27
Jokkmokk	4 750	23	48±19
Gallivare	12 911	41	36±11
Kiruna	14 129	64	55±13
Total	374 544	2 590	59±2

cinoma seems to be more frequent in urbanized and industrialized regions and in populations with high socioeconomic status but these conditions may of course be correlated to other factors such as birth rate and dietary habits Rare etiologic factors are ionizing radiation (MACKENZIE 1965 WANEBO et coll 1968) and possibly some drugs such as reserpine (ARMSTRONG et coll 1974)

Among the more basic theories for development of breast carcinoma those based upon hormonal and viral mechanisms are the most prominent The hormonal theory has mainly concerned the observation that patients with breast carcinoma and populations at high risk for this type of tumour may have a reduced urinary estriol/estrone estradiol quotient and an increased prolactin activity (cf LEMON 1976 WYNDER et coll 1976) The virus theory emanates from the well known mammary tumour virus in mice and there is also some evidence for markers of RNA tumour viruses in human mammary carcinoma (cf SCHLOM 1976) Since human breast carcinoma may well be caused by multiple factors neither of these theories excludes the influence of other factors such as heredity marital status parity and dietary habits There could also be a physiologic link between some of the causative factors An example of that may be an observed correlation between the dietary fat content and the prolactin level (CHAN et coll 1975 HILL & WYNDER 1976)

Geographic subdivision The three northernmost counties in Sweden constitute an area of 178 462 km and stretch from 69 to 62 latitude The county is the unit for state administration and also for health care (through the county council) Using the historical subdivision of Sweden each county was further divided into two provinces Vasternorrland County (Y county) into Medelpad and Ångermanland Vasterbotten County (AC county) into Vasterbotten and S Lappland and Norrbotten County (BD county) into Norrbotten and N Lappland The small differences which exist between the borders of counties and provinces were hereby neglected and Lappland was divided into 2 provinces The *municipality* in Sweden is a unit for local government administration The subdivision in municipalities has been

rath r radically changed during the period analysed with the general intention being to obtain larger municipalities As one new municipality corresponds exactly to one or several previous municipalities it was however possible to obtain homogenous d mographic data for the entire period

The borders for counties provinces and municipalities are presented in Fig 2 and their mean female populations in Table 2 Within this area the Baltic coastal region is the most densely populated while the inner part of the area is much less populous (Table 2)

Material and Methods

The Swedish Cancer Registry was started in 1958 and yearly reports have been published up to 1971 Data from the first year 1958 is regarded as somewhat un reliable due to lack of experience among reporting institutions and was therefore omitted in the present analysis The register is based upon compulsary reports of new cases of malignant tumours from all hospitals and pathology departments

Lists of all cases of female breast carcinoma within the studied region were obtained from the Registry for the period 1959 to 1971 This regional register contained a code for county but not for municipality or parish and the addresses for the patients at the time of registration had to be found by sending questionnaires to the county population registries hospitals and parish authorities The original lists contained 2 691 cases a figure which was reduced to 2 590 cases for the final analysis The reasons for this reduction were double registration erroneous county coding reg istration of secondary manifestation of previously registered breast carcinoma and — in 23 cases—the fact that the addresses of the patients could not be found A carcinoma in the remaining breast was by definition regarded as a secondary mani festation of the first breast carcinoma The reduction in the number of ca es was only 3 7 per cent and did not reduce the possibility of comparing incidence rates in the region analysed with those from other parts of the country for which only the uncorrected figures from the Swedish Cancer Registry could be used

The reliability of the regional register was further tested in one of the counties namely Vasterbotten County The local registries in the departments of surgery radiation therapy cytology and pathology were compared with the corrected li t from the Swedish Cancer Registry (765 cases) Only 4 cases were found that were erroneously included in the list and additionally 4 cases were found to be lacking in the list in which they should have been included This marginal discrepancy was neglected

For calculation of age adjusted incidence rates and age specific incidence rates demographic data were needed for the period 1959 to 1971 for the different geographic units These data were obtained from the National Census of Population which in Sweden usually is performed every fifth year The demographic data for the other years w re obtained by interpolation and extrapolation Four censu es were u ed for this pr cedure (1960 1965 1970 and 1975)

Table 3

Comparison between the observed distribution and computer simulated random distributions

Age standardized incidence 1959–71	Simulated						Observed
	1	2	3	4	5	6	
200–299							1
300–399							1
400–499		3		1	1	1	5
500–599	3		4	4	2	1	4
600–699	5	3	5	5	8	5	4
700–799	15	18	17	12	12	18	10
800–899	9	6	6	6	9	6	5
900–999	2	2	2	6	1	4	3
1 000–1 099		3	1		1		2
1 100–1 199	1			1	1		

For calculation of age adjusted incidence rates the female population for 1965 in the whole of Sweden was used as standard The incidence rates were calculated for the 13 year period from the number of carcinoma cases and the average female population during this period For easier comparison with figures in the literature the 13 year incidence rate was divided by 13, which gives approximately the average annual incidence rate during the period

The standard deviation for the age adjusted incidence rates was calculated according to a method described by CHIANG (National Office of Vital Statistics 1961) The 95 per cent confidence limits follow the ± signs

Results

The results for the different counties provinces and municipalities are presented in Table 2 The mean female population age adjusted incidence rate and 95 per cent confidence limits are given for each geographic unit

The age adjusted incidence rate for the entire region was 58 8 compared to 76 3 100 000 per year for the whole of Sweden The rate for the region was thus somewhat lower than in Sweden as a whole and it was essentially lower than that in the three largest cities (Malmo Goteborg Stockholm) which have the highest incidence rates reported in Sweden (Fig 1) However very great variations existed between different municipalities (Table 2 Fig 2) The general trend was a lower rate in the inner western part (border region to Norway) and the most northern part (border region to Finland) while the highest rates were registered for the eastern coastal region and especially for the southern part but exceptions from this general rule existed Two rather closely situated municipalities in Norrbotten had incidence rates which differed by a factor of 4 On the whole the variation in the incidence rate was sur

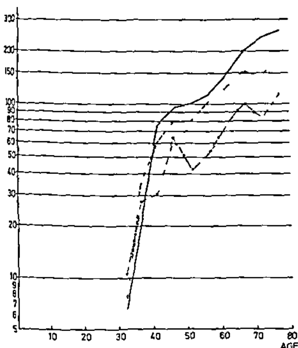


Fig 3 Age specific incidence curves for high incidence (——) medium incidence (---) and low incidence ( ) municipalities in northern Sweden

prisingly great and definitely greater than could be expected from pure random variation In 11 of the 35 municipalities the rates significantly differed from the incidence rate for the entire region and in 9 of these municipalities the deviation was towards a lower incidence

From knowledge of the mean age distribution in the different municipalities and the ages of the cases with carcinoma computer simulations were performed assuming a random distribution of the breast carcinoma cases between the municipalities The observed distribution was quite different from the simulated distributions with an obvious deviation in the low incidence direction (Table 3)

It was of interest to compare age specific incidences in different municipalities Age specific incidence curves for high incidence medium incidence and low incidence municipalities in these counties appear in Fig 3 All curves show the peculiar hook around the age of menopause as first described by CLEMMESEN (1948) For the low incidence municipalities a bimodal curve was obtained and the most marked difference between low incidence and high incidence municipalities concerned the postmenopausal age

The annual crude incidence and adjusted incidence rates for the period 1959 to 1971 were calculated for the whole of Sweden for the entire region analysed and for each of the three counties (Fig 4) Assuming an exponential distribution of the figures the crude incidence increased by about 3 per cent per year and the age adjusted incidence by about 1 5 per cent per year both in the whole of Sweden and in

Table 3

Comparison between the observed distribution and computer simulated random distributions

Age standardized incidence 1959–71	Simulated						Observed
	1	2	3	4	5	6	
200–299							1
300–399							1
400–499		3		1	1	1	5
500–599	3		4	4	2	1	4
600–699	5	3	5	5	8	5	4
700–799	15	18	17	12	12	18	10
800–899	9	6	6	6	9	6	5
900–999	2	2	2	6	1	4	3
1 000–1 099		3	1		1		2
1 100–1 199	1			1	1		

For calculation of age adjusted incidence rates the female population for 1965 in the whole of Sweden was used as standard The incidence rates were calculated for the 13 year period from the number of carcinoma cases and the average female population during this period For easier comparison with figures in the literature the 13 year incidence rate was divided by 13 which gives approximately the average annual incidence rate during the period

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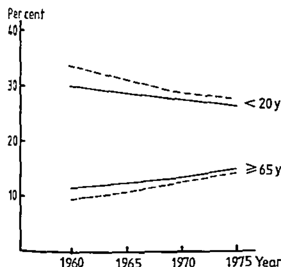


Fig 5 Comparison between distribution of age in the whole of Sweden (——) and in the three northernmost counties Y AC BD (-—)

part of the region has more slowly adjusted to a modern life style than has the more urbanized coastal area Similar differences may have existed as regards dietary habits

Regardless of the possible explanations it is interesting that such large differences in the incidence of breast carcinoma can be found within such a limited and relatively homogeneous population The lowest incidences observed are comparable to those in extremely low incidence regions such as in Japan and the highest incidences to those in high incidence regions such as in western Europe

A thorough analyses of all factors known to influence the development of breast carcinoma could be of interest within different municipalities in northern Sweden but it may be too late life styles have rapidly changed and it is likely that the differences now are much smaller than they were when the women in the present analysis were influenced—or not influenced—by breast carcinogenic factors

Acknowledgements

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SUMMARY

The age standardized incidence rates for female breast carcinoma were calculated for the 3 northernmost counties in Sweden and their municipalities for the period 1959 to 1971 Large variations were found that could not be explained by random distribution Lower

incidences were encountered in the less urbanized municipalities in the western and northern parts The largest relative difference between low incidence and high incidence municipalities concerned the post menopausal period

ZUSAMMENFASSUNG

Die Alters standardisierte Frequenz des Vorkommens von weiblichen Brustkarzinomen fur die drei nordlichst gelegenen Bezirke Schwedens und deren Gemeinden fur die Periode *1959* bis *1971* wurde berechnet Grosse Variationen wurden gefunden *die nicht durch eine* zufallige Verteilung erklart werden konnen Ein niedriges Vorkommen wurde in den weniger urbanisierten Gemeinden in den westlichen und nordlichen Teilen festgestellt Die grössten relativen Unterschiede zwischen niedrig und haufig vorkommenden Gemeinden betraf die Periode nach der Menopause

RÉSUME

Les taux de frequence standardises en fonction de l age pour le carcinome du sein de la femme ont été calculés pour les trois provinces les plus septentrionales de la Suède et pour leur municipalite pendant la periode allant de 1959 à 1971 Les auteurs ont trouve de larges variations qui ne peuvent pas etre expliquées par une distribution aléatoire Ils ont trouvé les plus basses frequences dans les municipalites les moins urbanisées dans les parties occidentales et septentrionales La plus grande différence relative entre les municipalités à faible fréquence et celles à haute frequence à concerné la periode post ménopausique

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BIOGENIC AMINE RESPONSE TO WHOLE BODY IRRADIATION

Prevention by APTH

G C PRASAD S S HASAN S N PANDEYA S MAZUMDAR and P M SINGH

It is a well documented fact that irradiation brings about marked disturbances in the bioamine levels (NAIR 1965 BRINKMAN & VENINGA 1962 VENINGA & DE BOER 1963 VARAGIC et coll 1967) The bioamine levels have furthermore been correlated with mortality by SIMMSON et coll (1970) MATHEW (1973) and MODIGH (1974) They have also claimed that any drastic change in the bioamine levels proves to be lethal However the role of bioamines in connection with the use of a chemical radiation protector are still obscure and need to be probed further

Unpublished data indicate marked changes in the bioamine levels followed by a 50 per cent mortality 15 days post irradiation This motivated a search for a drug which could diminish the post irradiation changes and prevent the mortality The influence of a radiation protective drug on the functional condition of certain biogenic amines of brain and blood was investigated The experiments were also designed to throw light on the response of hypothalamic neurosecretory neurons to radiation

Material and Methods

Ninety albino rats weighing 100 to 110 g were used They were acclimatised for two weeks to laboratory conditions prior to commencement of the experiments During the acclimatisation and experimental periods the animals were fed on balanced

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laboratory diet procured from Hindustan Livers Ltd (Bombay India) and water was permitted ad libitum 1 acetyl 3 phenylamidine thiocarbamide hydrochloride (APTH) a newly synthesized organic compound (by S N P) was used as a radiation protector This compound is formed by interaction of phenylamidine chloride with N acetyl thiocarbamide It i a derivative of amidine thiocarbamide which i a sulphur containing compound The LD_{50} of the drug (intraperitoneal injection) exceeded 90 0 mg/kg body weight

The experiments were carried out in 3 different groups each containing 30 rats

Group I received 1 ml physiologic saline and served as normal controls

Group II received 1 ml of physiologic saline and was exposed to 154 8 mC/kg (600 R)

Group III received APTH 3 mg/100 g and was also exposed to 154 8 mC/kg

The solution of APTH in physiologic saline was freshly prepared before testing to a pH of 9 0 The solution was injected intraperitoneally 30 min before irradiation with ^{60}Co The rats in group II were irradiated simultaneously with the APTH treated rats and thereafter housed under identical conditions

The mortality rate was recorded over a period of 30 days The animals were killed at day 15 or day 30

The brains were dissected out and were fixed in Bouin s fluid The sections were 10 μ thick and were stained in Gomori s aldehyde fuchsin after Halmi s modification for the demonstration of neurosecretion

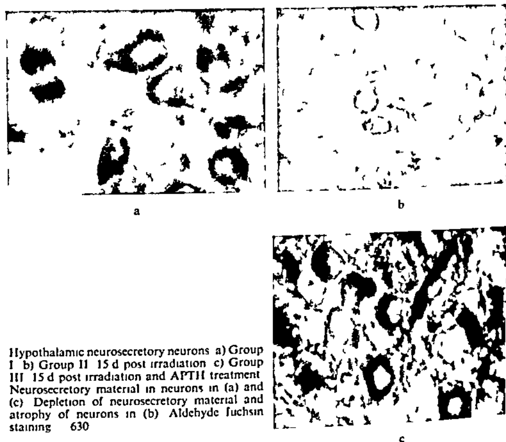
The blood from each animal was collected in a heparinised tube and subjected to biochemical analysis of acetylcholine (Pandey et coll 1975) and cholinesterase (Caraway 1956) The whole brain was removed and transferred to a solution of 0 4 N perchloric acid ($HClO_4$) After homogenisation 5 HT (Snyder et coll 1965) and catecholamine (Crout 1961 with certain modifications) were extracted and estimated fluorometrically

Results

Group II had an overall mortality of 60 per cent within a month of those 50 per cent occurred within the first two weeks In groups I and III no mortality was recorded during this period

Hypothalamic neurosecretory neurons In group II a complete depletion of neurosecretory materials was found with a consequential reduction in the size of neurons (Fig b) In groups I and III the neurons behaved identically and had a fair amount of neurosecretory material the size of the neurons in groups I (Fig a) and III (Fig c) not being reduced

Brain hydroxytryptamine (5 HT) (Table 1) On day 15 the brain 5 HT level following irradiation had decreased significantly to 0 404 μg/g from the group I level of 0 591 μg/g (p 0 001) whereas in group III the level rose to 0 799 μg/g In com



Hypothalamic neurosecretory neurons a) Group I b) Group II 15 d post irradiation c) Group III 15 d post irradiation and APTH treatment Neurosecretory material in neurons in (a) and (c) Depletion of neurosecretory material and atrophy of neurons in (b) Aldehyde fuchsin staining 630

parison with group I this was not highly significant (p 0 025) At day 30 the 5 HT level had increased to 0 724 μg/g which was statistically insignificant (p 0 05) in comparison with the group I value of 0 539 μg/g In group III the 5 HT level further increased to 0 899 μg/g which was statistically significant (p 0 01) in comparison with group I but remained insignificant (p 0 05) in comparison with group II (Table 1)

Brain catecholamine (Table 2) On day 15 after irradiation the brain catecholamine level had decreased to 0 811 μg/g which was statistically significant (p 0 025) in comparison with the group I value of 1 194 μg/g whereas in group III the level increased significantly to 1 934 in comparison with groups I and II (p 0 05 and p 0 01 respectively) On day 30 following irradiation the catecholamine level had decreased to 0 615 μg g which was statistically significant (p 0 01) as compared to group I (1 163 μg g) while in group III the catecholamine level showed a little rise (1 810 μg/g) significance level p 0 05 in relation to group I p 0 001 in relation to group II

Table 1

5-hydroxytryptamine content (μg/g) in the brain tissue of control animals (group I) irradiated controls (group II) and drug treated irradiated animals (group III)

Day 15			Day 30		
Group I	Group II	Group III	Group I	Group II	Group III
0 591 SD ±0 148	0 404 SD ±0 016	0 799 SD ±0 048	0 539 SD ±0 212	0 724 SD ±0 301	0 899 SD ±0 202

Table 2

Catecholamine content (μg g) in the brain tissue in group I II and III

Day 15			Day 30		
Group I	Group II	Group III	Group I	Group II	Group III
1 194 SD ±0 432	0 811 SD ±0 268	1 934 SD ±1 029	1 163 SD ±0 501	0 615 SD ±0 144	1 810 SD ±0 09

Table 3

RBC acetylcholine and cholinesterase of groups I II and III

	Day 15			Day 30		
	Group I	Group II	Group III	Group I	Group II	Group III
RBC Acetylcholine (μg/ml)	0 990 SD ±0 321	0 926 SD ±0 169	2 105 SD ±0 5[illegible]1	0 828 SD ±0 415	0 972 SD ±0 [illegible]77	2 1 0 SD ±0 476
RBC Cholinesterase (PU/ml)	79 00 SD ±4 95	37 50 SD ±3 62	56 00 SD ±5 20	82 01 SD ±1 39	51 00 SD ±4 18	79 50 SD ±8 10

RBC acetylcholine (Table 3) In group II the acetylcholine level on day 15 had decreased to 0 926 μg/ml as compared to group I (0 990 μg/ml) which was statistically insignificant ($p < 0.05$) whereas in group III the acetylcholine level rose to 2 105 μg/ml which was highly significant ($p < 0.001$) in comparison with groups I and II On day 30 after irradiation the acetylcholine level increased to 0 972 μg/ml which was in significant ($p < 0.05$) in comparison with group I (0 828 μg/ml) In group III the level increased significantly ($p < 0.001$) to 2 120 μg/ml in relation to groups I and II

RBC cholinesterase (Table 3) On day 15 the cholinesterase level had decreased significantly (37 50 PU/ml $p < 0.001$) in group II in comparison with group I (79 0

PU/ml) In group III the cholinesterase level increased and was highly significant ($p < 0\ 001$) in comparison with groups I and II On day 30 the cholinesterase level was found to be significantly lower in group II ($p < 0\ 001$) in comparison with group I whereas in group III the cholinesterase further increased in comparison to group II it was statistically significant ($p < 0\ 001$) but insignificant in comparison to group I ($p < 0\ 05$)

Discussion

The results clearly demonstrate a mortality of 60 per cent within 30 days after 154 8 mC/kg (600 R) ^{60}Co irradiation but after treatment with APTH with a dose of 3 mg/100 g no deaths occurred BONEFI & NUVOLONE (1958) recorded a 26 to 44 per cent survival after cysteamine acetic acid and N glutanyl cysteamine before ir radiation with 600 R *A similar observation was made by* FOYE & MICKELS (1962) using 2 piperazinoethyl dithiocarbamic acid Hence APTH is more effe tive at this radiation dose

The irradiation eliminates neurosecretory material from the perikaryons of the neurons and causes a marked atrophy of the nuclear volume of the supraoptic and paraventricular neurons When the rats were irradiated 30 min after the injection of APTH the neurons were still found loaded with neurosecretory material and no nuclear atrophy was observed It seems that the drug counteracts the effect of ir radiation This agrees well with previous observations of DUCHESNE et coll (1968)

It has been observed that irradiation causes a marked disturbance in the biogenic amine levels *In the present series irradiation decreased the* 5 hydroxytryptamine (5-HT) and catecholamine (CA) contents of the brain during the fir t two weeks the p riod with maximum mortality After administration of APTH before irradiation the bioamine lev l was similar to that in the controls After day 15 when the mortality i lower the 5 HT was a little higher than in the controls This may be attributed to a compensatory phenomenon in order to raise the decreased level of 5 HT This partly substantiates the findings of BACQ et coll (1954) They found normal content of cholesterol and ascorbic acid in the adrenals of protected rat 3 days after irradia tion

It was further observed that acetylcholine in the APTH treated group increased as well as did cholinesterase *It suggests that acetylcholine in the tr ated group is* l ke other biogenic amine required in exce quantity Probably the synthesi in creases after APTH administration although the degradation rate as indicated by the increased level of cholinesterase remains higher Under such condition it seems probable that the synthesis i much higher than the degradation and hence acetyl choline and cholinesterase levels remain increased

On the basis of these results it is suggested that the irradiation protective property of APTH is cau ed by stimulating the synthesis of bioamines It also supports the assumption that it counteracts the action of protein depletion owing to io izing radiation which in turn further corraborates the findin of DUCHESNE et coll

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SUMMARY

Co whole body irradiation with 154 8 mC/kg (600 R) resulted in a mortality of 50 per cent within two weeks Administration of 1 acetyl 3 phenylamidine thiocarbamide hydrochloride (APTH) 30 min before irradiation prevented this mortality Irradiation eliminated neurosecretory material from the perikaryons of the supraoptic and paraventricular neurons whereas APTH counteracted this action APTH also increased the synthesis of bioamines (5 hydroxytryptamine catecholamine and acetylcholine)

ZUSAMMENFASSUNG

Co Ganzkorperbestrahlung mit 154 8 mC/kg (600 R) fuhrte zu einer Mortalität von 50 Prozent in 2 Wochen Die Gabe von 1 Acetyl 3 Phenylamidin Thiocarbamid Hydrochlorid (APTH) 30 Minuten vor der Bestrahlung verhinderte diese Mortalität Die Bestrahlung eliminierte neurosekretorisches Material von den Perikaryons der supraoptischen und paraventrikularen Neuronen wobei APTH diesem Effekt entgegenwirkt APTH steigerte auch die Synthese de Bioamine (5 Hydroxytryptamin Catecholamin und Acetylcholin)

RESUME

L irradiation du corps entier par le Co avec 154 8 mC kg (600 R) a donné une mortalité de 50 en deux semaines L administration d hydrochlorure de 1 acétyl 3 phénylamidine thiocarbamide (APTH) 30 minutes avant l irradiation a empeché cette mortalité L irradiation a éliminé le materiel neurosecretoire des perikaryons des neurones supra optiques et para ventriculaires alors que l APTH contrarie cette action L APTH augmente aussi la synthese des bioamines (5 hydroxytryptamine catecholamine et acétylcholine)

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RELATION BETWEEN SEVERITY OF THYROTOXICOSIS AND RESPONSE TO ¹³¹I THERAPY

K J OLSEN H E NIELSEN and H HVID HANSEN

Treatment of hyperthyroidism with ¹³¹I is certainly efficacious and simple but has some disadvantages the most important being a delay in achieving control of the disease possible recurrences difficulty in predicting the outcome and a significant incidence of hypothyroidism (MALONE 1975 WERNER 1971) The risk of late hypo thyroidism is due to difficulty in determining the radiation dose to the thyroid (FALKEN SAMMER et coll 1975 MALONE & CULLEN 1975 WERNER) and to apparently large biologic variation in sensitivity of the thyroid to radiation This has led to recommendations to lower the dose which however leads to a further delay in control of the disease without diminishing the risk of late hypothyroidism (CEVALLOS et coll 1974 MALONE WERNER)

An analysis of the results of ¹³¹I therapy in this department was performed in an attempt to find bio chemical parameters related to the response to the therapy

Material and Methods

The material consisted of 36 females with a mean age of 60 years (range 29-85) and 9 males with a mean age of 60 years (range 48 74) treated for hyperthyroidism between August 1974 and January 1977 Most of the patients were referred to treat ment with ¹³¹I because control of the disease was not obtained by surgery or anti

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thyroid drugs Previously 38 patients had been treated with antithyroid drugs and 13 had been operated upon Only 7 patients had no previous antithyroid treatment

The thyroid clearance was determined from uptake valu s at 1 and 2½ h and the blood level of ^{131}I at 1¾ h after oral administration to the fasting patients Absolute iodine uptake (AIU) was calculated from the thyroid cl arance the sp cific activity of ^{131}I in the urine and the level of ^{131}I in the blood (ALEXANDER et coll 1964) Uptake values at 24 48 and 72 h were used to determine the effective half life of ^{131}I in the thyroid

The amount of functioning thyroid tissue was calculated from scintigraphy at 24 h after the administration of ^{131}I It was assumed that the thyroid had the shape of an ellip oid and that the width and thickness of each lobe were equal

The radiation dose to the thyroid from ^{131}I was calculated from the expression $D(Gy) = 1\ 56 \times (A \times a \times T_{eff})/W$ with $A = mCi$ ^{131}I administered a – per cent uptake at 24 h T_{eff} = effective half life (days) of ^{131}I and W = weight of gland in gram The formula was derived from the MIRD table (Medical Internal Radiation Dose Committee 1969) by taking ϕ = fractional absorption of the γ rays from ^{131}I 0 05 (THOMAS et coll 1977) and assuming a monoexponential disappearance of ^{131}I from the thyroid

Serum T_4 levels were measured with a competitive protein binding assay while T_3 and TSH were determined with radioimmunoassays Free fractions of T_4 and T_3 were measured by a dialy is method (PEDERSEN 1974)

Statistical methods The Mann Whitney rank sign test for unpaired comparisons of group means and the chi square test were used

Results

The 45 patients received 71 doses of ^{131}I 29 receiving one 7 two 8 three and one four doses The average dose per treatment was 100 Gy or 8 6 mCi ^{131}I The pati nts were divided into 3 groups according to the effect of the therapy at an observation time of 6 to 12 months after the last treatment Group 1 hypothyroid patients with need of hormone replacement Group 2 euthyroid patients Group 3 hyperthyroid patients with need of antithyroid drugs The group 1 patients all developed hypothyroidism within 3 months after the iodine treatment

Clinical data for the 3 patient groups are given in Table 1 and biochemical data before treatment in Table 2 The age of the patients in group 1 was significantly lower than in groups 2 and 3 (p 0 01) In group 3 the thyroid gland was significantly larger than in groups 1 and 2 (p 0 02) No difference was found between the groups in the frequency of p i nts previously operated upon or treated with antithyroid drugs or in the frequ r f nodular or diffuse enlargement of the gland The severity of thyrotoxicosis eval ted by measuring the serum concentration of free and total thyroid hormores di t differ between the groups

Table 1

Clinical data for 45 hyperthyroid patients before treatment with ¹³¹I

	Group 1	Group 2	Group 3
Number of patients	7	13	25
Age mean (range)	51 4 (40–60)	66 1 (49–83)	64 6 (49–85)
Previously operated	4	4	5
Previously antithyroid drugs	7	10	21
Diffuse goiter	6	5	20
Nodular goiter	1	8	5
Gland weight (g)	30	3_	48
Thyroid antibodies	3 of 4	3 of 10	5 of 22

Table 2

Biochemical data in 45 hyperthyroid patients before treatment Mean and range given in parentheses

	Group 1	Group 2	Group 3	Normal range
T_4 (nmol/l)	158 (7_–218)	162 (113–219)	190 (67–350)	72–140
Free T_4 (pmol/l)	69 (28–96)	75 (_8–127)	107 (18–609)	31–54
T (nmol/l)	3 01 (2 22–3 59)	2 77 (1 90–4 05)	3 50 (1 68–6 54)	1 16–2 32
Fr e T (pmol/l)	17 7 (9 8–24 ?)	18 3 (8 4–33 0)	8 6 (8 7–105)	6 9–13 6

In 29 patients thyroid clearance and AIU were measured The biochemical data for these patients are given in Table 3 The division of the patients in groups follows the same criteria as in Tables 1 and 2 The AIU and gland size was significantly higher ($p<0\ 01$ and $p<0\ 02$ respectively) in group 3 than in 1 and 2 No significant difference was found between the other biochemical values

The total radiation dose to each patient in the groups the total amount of mCi ¹³¹I and the ratio between AIU before treatment to the total radiation dose appear in Table 4 No significant difference between the dose in Gy and mCi given was found However the ratio between the total dose and AIU was significantly higher ($p<0\ 01$) in groups 1 and 2 than in group 3

Discussion

The results suggest a relation b tween the degree of hyperfunction of the thyroid gland measured by the AIU and the radiation dose needed to reduce the function to normal level The connection between the severity of the hyperfunction and the

Table 3

Biochemical data including AIU in 29 hyperthyroid patients before treatment Mean and range in parentheses

	Group 1	Group 2	Group 3	Normal range
Number of patients	6	7	16	
T_4 (nmol/l)	163 (78-218)	163 (113 219)	203 (67-350)	7? 140
Free T_4 (pmol/l)	69 (28-96)	76 (34 127)	133 (18-609)	31 54
T_3 (nmol/l)	3 17 (2 52-3 59)	2 78 (1 90-4 05)	3 96 (1 91-6 54)	1 16-? 3?
Free T_3 (pmol/l)	19 3 (10 4-24 2)	20 0 (9 2-33 0)	36 0 (11 5 105)	6 9 13 6
Thyroid clearance (ml/min)	141	84	181	10 60
AIU (μg/h)	5 40 (1 62-10 8)	5 63 (1 09-9 44)	19 7 (4 38 84 7)	1 0 5 0
Gland weight (g)	31 (15-45)	34 (15-50)	55 (0 1_0)	
$T_{\frac{1}{2}}$ effective (days)	4 1 (3 1 6 3)	5 2 (3 2-8 0)	5 4 (3 1 8 0)	
24 hour uptake of ^{131}I ( )	71 (58-81)	61 (44-77)	(5 (37 78)	30 65

radiation dose necessary for control has been suggested previously but no corroborating evidence has been presented (WERNER)

The need for higher doses to control severe hyperfunction may simply be explained by a relationship between the number of cells inactivated by irradiation and the dose as found in survival curves for irradiation of cells (MALONE) In severe hyperthyroidism and in cases with large thyroid glands a larger number of cells must be destroyed or inactivated

AIU is closely related to the production of thyroid hormones (RAPOPORT & DE GROOT 1971) if patients with dyshormogenesis are excepted although it overestimates the hormone production because correction is not made for the leakage of iodide and production of iodoproteins (OLSEN & HANSEN 197(RAPOPORT & DE GROOT) AIU is a better measure of gland function than the level of circulating thyroid hormones both total and free since the hormone level in serum d p nds on both production degradation and distribution volume

The risk of late hypothyroidism is not further dealt with in the present discussion However a fairly high proportion (7/45) of the patients developed hypothyroidism

Table 4

Total radiation dose and radiation dose per AIU unit in 29 hyperthyroid patients before treatment Mean Range in parentheses

	Group 1	Group 2	Group 3
Gy	193 (62–436)	113 (59–230)	147 (68–372)
MBq	377 (225–537)	317 (142–803)	921 (124–2 516)
mCi	10 2 (6 09–14 5)	8 58 (3 84–21 7)	24 9 (3 34–68 0)
Gy/AIU	50 7 (10 4–98 8)	36 1 (10 0–147)	12 3 (3 4–37 2)

within 3 months after treatment This may be due to higher radiation dose and to thyroid antibodies present in these patients (LUNDELL & JONSSON 1973)

Although the radiation dose is similar in all 3 groups the ratio between dose and AIU was higher in groups 1 and 2 compared with group 3 Too few results from measurements of circulating antibodies are available to test the significance of autoimmune hypothyroidism

The group 1 patients are younger than the patients in groups 2 and 3 This may be related to the fact that older people are more resistent to developing hypo thyroidism after iodine therapy (WERNER)

The radiation dose calculated from the formula given may be erroneous due to the method used for estimating the gland size and the assumption of a monoexponential disappearance of ^{131}I from the thyroid The size is probably overestimated due to the limited resolution of the scanning equipment (OLSEN 1978) The error will be larger for small glands i e the doses in groups 1 and 2 are probably larger than those given in Table 4 This will further accentuate the difference between group 3 and groups 1 and 2

Liberation of iodine due to degradation of thyroid hormones containing ^{131}I will also increase the doses relative to those given in Table 4 since some of the ^{131}I is recirculated to the thyroid This correction is important in cases with fast iodine turnover (MALONE & CULLEN 1975) i e small effective half life of ^{131}I The effective half life of ^{131}I does not differ significantly in the 3 groups The correction for recirculation will be small and without effect on the difference between the groups

The average dose of 100 Gy at each treatment is similar to the dosage scheme of GLANZMANN et coll (1975) They found that 75 per cent of the patients could be controlled by a single dose of about 100 Gy but they used a slightly different formula for calculating the dose increasing the calculated dose 15 per cent relative to the

calculation in the present series The low success rate in the present series may be explained both by the fact that the patients were fairly old and that the majority of patients had responded unsatisfactorily to surgery or treatment with thyrostatic drug

The gland of the poor responders group 3 was larger than in the other groups but the significance of this fact is at present not known GLANZMANN et coll used a higher dose for large glands (>60 g)

In conclusion the present results indicate a relation between the severity of hyperthyroidism and response to ^{131}I therapy It is desirable that this finding should be analysed in a larger material than the present one

SUMMARY

The relation between the severity of hyperthyroidism and response to ^{131}I therapy was tested in a group of 45 patients 6 to 12 months after therapy At following treatment 7 patients were hypothyroid 13 euthyroid and 25 hyperthyroid The absolute iodine uptake and gland size was significantly higher in the hyperthyroid group compared with the other groups The radiation dose was similar in the groups but the ratio between dose and uptake was significantly lower in the hyperthyroid group

ZUSAMMENFASSUNG

Der Zusammenhang zwischen dem Grad des Hyperthyreoidismus und der Antwort auf ^{131}I Therapie bei einer Gruppe von 45 Patienten 6 bis 12 Monate nach der Therapie wurde untersucht Im Anschluss an die Behandlung waren 7 Patienten hypothyreoid 13 euthyreoid und 25 hyperthyreoid Die absolute Jodaufnahme und die Thyreoideagrösse waren signifikant höher in der hyperthyreoiden Gruppe verglichen mit den anderen Gruppen Die Strahlendosis war gleich in diesen Gruppen jedoch war das Verhältnis zwischen Dosis and Jodaufnahme signifikant niedriger in der hyperthyreoiden Gruppe

RÉSUMÉ

La relation entre la gravite de l hyperthyroïdie et la reponse au traitement par ^{131}I a été testée sur un groupe de 45 malades de 6 à 12 mois après le traitement A un traitement ultérieur 7 malades etaient hypothyroïdens 13 euthyroïdiens et 25 hyperthyroïdiens La fixation totale d iode et le volume de la glande étaient significativement plus élevés dans le groupe hyperthyroïdien que dans les autres groupes La dose de radiations etait semblable dans ces groups mais le rapport entre la dose et la fixation était significativement plus bas dans le groupe des hyperthyroïdiens

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HISTIOCYTOSIS X

IV—Immunologic response assessed by lymphocyte transformation tests

P. THOMMESEN, P. FREDERIKSEN and F. JORGENSEN

Histiocytosis X is a disease mostly of early childhood characterized by proliferation of differentiated histiocytes. Neoplastic or infectious factors have been considered initiating causes, but at the present time the etiology remains unknown (VOGEL & VOGEL 1972).

The microscopic findings in thymus and in peripheral lymphoid tissue in fatal cases have suggested the existence of immunologic abnormalities at least in some patients (OCHS et coll. 1974, CEDERBAUM et coll. 1974, ENRIQUEZ et coll. 1976).

LEIKIN et coll. (1973) found in patients with active histiocytosis X that had been given chemotherapy no evidence of an immunodeficiency disorder. The few abnormalities observed were regarded as secondary to malignant cell replacement.

In an attempt to disclose a possible immunologic disturbance, lymphocyte transformation tests were performed in children with histiocytosis X in whom remission was obtained without chemotherapy.

The immune system is divided functionally into two collaborating parts (COOPER et coll. 1968), whose cellular elements are partly composed of the thymus-dependent T lymphocytes and the thymus-independent B lymphocytes. Their unspecific reactivity can be assessed in vitro by stimulation with certain plant mitogens, e.g. PHA, PWM and Con A, and more immunospecific testing is achieved by the MLC test (mixed lymphocyte cultures). PHA, Con A and MLC responsiveness is a T lymphocyte characteristic (JANOSSY & GREAVES 1972, HAYRY & DEFENDI 1976), whereas B lymphocyte characteristics are MLC stimulatory capacity (HAYRY & DEFENDI) and partly PWM responsiveness (JANOSSY & GREAVES).

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Table 1

Si ri ey of 8 patients with histioci tosis X

Case	Age at onset (years)	Age tested (years)	Organ system involved	Present condition	Previous treatment	Pı treaunent
1	1	2	Skeleton	Remı sion	Irradiation	None
2	2	6	Gingival mucosa pituitary	Remission	Irradiation insipidin	Insipidin
3	3	6	Gingival mucosa, temporal bone	Remission	Irradiation	None
4	7	10	Skeleton	Remission	Surgery irradiation	None
5	5	9	Skeleton	Remission	None	None
6	2	6	Skeleton lungs subcutaneous	Remission	Irradiation prednisone	None
7	2	6	Skeleton cranium	Remission	Irradiation prednisone	None
8	2	6	Skeleton gingival mucosa pituitary	Active disease	Irradiation pred nisone insipidin	Prednisone insipidin

Material and Methods

Eight control pairs consisting of boys unmatched as to age were included (Because the patients were children it was impossible to obtain controls of similar sex and age) Of the eight patients 6 were examined twice and 4 were examined a third time The repetitive blood samples were taken several months apart and the lymphocytes were isolated frozen and stored in nitrogen vapour until all the specimens were collected and the testing was performed

The microscopic diagnosis of histiocytosis X was achieved in all patients as previously described (FREDERIKSEN & THOMMESEN 1978)

Hemoglobin ESR leukocyte counting differential blood cell counting and serum electrophoresis were assessed by standard techniques Quantitative immunoglobulin determination was performed by the method of LAURELL (1966)

The basic lymphocyte culture technique has been described in detail (JORGENSEN & LAMM 1974) Phytohemagglutinin (PHA Wellcome) was used at final dilutions of 1 100 1 1 400 and 1 1 600 pokeweed mitogen (PWM Gibco) at 1 1 609 1 6 400 and 1 25 000 and finally concanavalin A (Con A Pharmacia Fine Chemicals) was used at 25 μg 6 μg and 1 5 μg per ml MCL reactivity was evaluated by testing the individuals as responders against three pools (A B C) of irradiated lymphocytes each from 3 individuals stimulating capacity was tested using their irradiated cells as stimulators against the cells from 4 normal test individuals Fifty thousand responding lymphocytes were used in mitogen stimulated cultures and 50 000 responding and 50 000 stimulating lymphocytes were cultured for MLC

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When used as stimulator cells in MLC the cells from the patients did not deviate in any systematic way from the controls and the average response elicited in each of the 4 responders of the patients was the same as of the controls (data not shown) The response capacity in MLC may be slightly lower in the patients compared to the controls the patient average against each pool being lower than the control average but without statistical significance (Table 2 Part 2)

One patient (No 8) behaved differently Concomitant with an aggrevation of the disease a marked but insignificantly increased response appeared in all test systems as compared to the patients with inactive disease and the controls (lower line in each part of Table 2)

Discussion

None of the patients received chemotherapy and only one was treated with prednisone during the investigation period No changes of the immunoglobulins compared to the controls were detected Likewise lymphocyte transformation tests (PHA PWM and Con A) in the 7 patients with inactive disease and in good clinical condition were found within normal limits Accordingly no basic immuno deficiency could be demonstrated Thus these findings support the observations of LEIKIN et coll

However a statistically non significant subnormal average response of the patient lymphocytes in the MLC test was noted This may indicate a disturbance in at least a fraction of the T cells e g either a deficit of allogeneic reacting T lymphocytes or an increased amount of suppressor T cells (MCMICHAEL & SASAZUKI 1977)

A possible pathogenetic significance of alterations of lymphocyte reactivity in vitro cannot pre ently be evaluated The normal (subnormal) responsiveness in remission seems difficult to reconcile with an increasing reactivity during relap e (Case No 8) It may be that some immunoregulatory dysfunction is of basic importance for development of histiocytosis X but such mechanisms can easily escape detection in vitro

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SUMMARY

Eight children with histiocytosis X were investigated with reference to immunologi reactivity in vitro (PHA PWM Con A and MLC testing) No significant impairment of immune function was detected but a subnormal (statistically insignificant) response in the MLC test may suggest some abnormality of the T lymphocytes reacting against allog neic cells In a patient who relapsed a marked but insignificant in rease in lymphocyte reacti ity in vitro was observed

ZUSAMMENFASSUNG

Acht Kinder mit Histiocytosis X wurden hinsichtlich ihrer immunologischen Reaktion in vitro (PHA PWM Con A und MLC Test) untersucht Keine signifikante Beeinträchtigung der Immunfunktion wurde entdeckt jedoch kann eine subnormale (statistisch nicht signifikante) Reaktion auf den MLC Test auf eine Abnormität der T Lymphozytenreaktion gegen allogene Zellen hinweisen Bei einem Patienten mit Rezidiv wurde eine kräftige jedoch nicht signifikante gesteigerte Lymphozytenreaktion in vitro beobachtet

RESUME

Huit enfants atteints d histiocytose X ont subi des examens concernant la réactivité immunologique in vitro (epreuves a PHA PWN Con A et MLC) On n a pas constaté de trouble de la fonction immunitaire mais une réponse subnormale (statistiquement non significative) à l epreuve MLC peut faire penser à une anomalie des lymphocytes T reagissant contre les cellules allogeniques Chez un malade qui a rechute on a observé une augmentation marquée mais non significative de la réactivite lymphocytaire in vitro

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